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(54) Title: METHODS FOR FORMING REGIONAL TISSUE ADHERENT BARRIERS AND DRUG DELIVERY SYSTEMS

(54) Titre: METHODES DE FORMATION DE BARRIERES ADHERENTES AUX TISSUS DANS DES ZONES DONNEES ET SYSTEMES D'ADMINISTRATION DE MEDICAMENTS

(57) Abstract

Methods are provided for forming hydrogel barriers in situ that adhere to tissue and prevent the formation of post-surgical adhesions or deliver drugs or other therapeutic agents to a body cavity. The hydrogels are cross-linked, resorb or degrade over a period of time, and may be formed by free radical polymerization initiated by a redox system or thermal initiation, or electrophilic-neutrophilic mechanism, wherein two components of an initiating sytem are simultaneously or sequentially poured into a body cavity to obtain widespread dispersal and coating of all or most visceral organs within that cavity prior to gelation and polymerization of the regional barrier. The hydrogel materials are selected to have a low stress at break in tension or torsion, and so as to have a close to equilibrium hydration level when formed.

(57) Abrégé

L'invention concerne des méthodes de formation de barrières d'hydrogel in situ adhérant aux tissus et empêchant la formation d'adhérences post-chirurgicales ou libérant des médicaments ou d'autres agents thérapeutiques dans une cavité corporelle. Les hydrogels sont réticulés, se résorbent ou se dégradent après une période déterminée et peuvent être formés par polymérisation de radicaux libres initiée par un système d'oxydoréduction ou une initiation thermique ou un mécanisme électrophile-neutrophile ; on introduit simultanément ou séquentiellement deux composants d'un système d'initiation dans une cavité corporelle pour obtenir une dispersion et un revêtement généralisés sur tous les organes viscéraux ou sur la plupart des organes à l'intérieur de cette cavité avant la gélification et la polymérisation de la barrière de zone. Les matières d'hydrogel sont sélectionnées de manière à présenter une faible contrainte de rupture à la tension ou à la torsion, et donc de manière à posséder un niveau d'hydratation proche de l'équilibre à leur formation.

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Description

METHODS FOR FORMING REGIONAL TISSUE ADHERENT BARRIERS AND DRUG DELIVERY SYSTEMS

Field Of The Invention

The present invention relates to methods of forming polymeric barriers to prevent post-surgical tissue adhesion and the use of such barriers to deliver drugs.

Background Of The Invention

The formation of post-surgical adhesions involving organs of the peritoneal cavity and the peritoneal wall is a frequent and undesirable result of abdominal surgery. Surgical trauma to the tissue caused by handling and drying results in release of a serosanguinous (proteinaceous) exudate that tends to collect in the pelvic cavity. If the exudate is not absorbed or lysed within a short time following the surgery, it becomes ingrown with fibroblasts. Subsequent collagen deposition leads to adhesion formation.

Numerous previously known methods have been developed to attempt to eliminate adhesion formation, but with limited success. Such methods include lavage

of the peritoneal cavity, administration of pharmacological agents, and the application of barriers to mechanically separate tissues. For example, Boyers et al., "Reduction of postoperative pelvic adhesions in the rabbit with Gore-Tex surgical membrane," *Fertil. Steril.*, 49:1066 (1988), describes the use GORE-TEX® (a registered trademark of W.L. Gore & Assocs., Inc., Newark, DE), expanded PTFE surgical membranes to prevent adhesions. Holtz, "Prevention and management of peritoneal adhesions," *Fertil. Steril.*, 41:497-507 (1984) provides a general review of adhesion prevention. None of the methods described in those articles has been cost effective and efficacious in in vivo studies.

Most adhesion prevention strategies have focused on either pharmacological approaches or barrier approaches. Pharmacological approaches have mainly relied on the local instillation of drugs such as antiinflammatory or fibrinolytic compounds. The advantage of the pharmacological approach is that the drugs can have not only a local but also a regional effect. The regional effect is particularly useful because, although iatrogenic injury is associated with adhesion formation, it is often difficult to predict all of the sites that may have been traumatized or exposed to ischemia during surgery. For example, during open surgical procedures, tissue often may be subjected to long periods of desiccation and surgical handling.

The word "local" as used herein is meant to connote a specific site on a tissue or organ surface, which for example is felt to be at risk for adhesion formation. The term "regional" as used herein, is meant to connote the general cavity or space within

which any of several organs are at risk for adhesion formation, but where it is for example, difficult to predict all the sites where such adhesions may form.

Instillation of drugs in regional spaces, such as the peritoneal cavity, has been widely adopted for the prevention of post-surgical adhesions. Unfortunately, most drugs administered in this fashion have a limited residence time at the site of instillation and are rapidly cleared. Also, delivery problems attributable to ischemia may reduce the effectiveness of the drugs. In addition, adhesions may develop not only due to surgical insults, but also due to a variety of pathologies and etiologies that may not be addressed using a pharmacological approach.

In view of the foregoing, it would be desirable to provide methods of preventing post-surgical tissue adhesion that overcome the drawbacks of previously known methods while providing the regional benefits obtained from pharmacological approaches.

Previously known barrier methods rely on the ability to interpose an inert or absorbable material in between organs at risk of formation of adhesions. A variety of materials have been used as barriers, including pentapeptides or elastin, trypsin treated gamma-irradiated amniotic membranes, polyesterurethane-polydimethylsiloxane, carboxymethylcellulose sponge, collagen etc. These previously known materials, however, have been used primarily in academic contexts and have not been developed as commercial products.

Commercially available local barriers, such as sold under the name INTERCEED™, a registered trademark of Johnson and Johnson, Inc., New Brunswick, NJ, SEPRAFILM™, Genzyme Corp., Cambridge, MA and REPEL™ under development by Life Medical Corp., Edison, NJ,

rely on interposing a barrier material that is absorbed within a 28 day period to reduce adhesion formation. These barriers, however, may have limited efficacy due to migration of the barriers from a local implantation site. Moreover, these barriers do not provide the regional effect observed with pharmacological barriers.

Barriers that may be applied as a liquid also have been used, such as hyaluronic acid based products such as SEPRACOAT™, marketed by Genzyme Corp., Cambridge, MA. U.S. Patent No. 5,140,016 to Goldberg et al. describes a method and composition for preventing surgical adhesions using a dilute solution of a hydrophilic polymer such as hyaluronic acid. U.S. Patent No. 5,190,759 to Lindblad et al. describes a composition and method for prevention of adhesions using solutions containing dextran and hyaluronic acid. These liquid barriers are rapidly cleared from a body cavity after instillation and thus may not be effective in preventing adhesions. Instead, such compositions are more effective as tissue protecting solutions during surgery rather than for the prevention of post-surgical adhesions.

Previously known attempts to prolong the residence of flowable barriers have attempted to form lightly crosslinked liquid barriers that still retain their flow characteristics. Thus, for example, LUBRICOAT™, available from Lifecore Biomedical Inc., Chaska, MN, is a ferric hyaluronate crosslinked slurry considered for adhesion prevention. This material has been found to have only limited efficacy, however, because the barrier tends to migrate from the application site. Thus, tissues that naturally appose each other still form adhesions.

Other natural and synthetic polymers also have been considered to prevent adhesion formation. U.S. Patent No. 5,605,938 to Roufa et al. describes methods and compositions for inhibiting cell invasion and fibrosis using dextran sulfate. The patent teaches that anionic polymers effectively inhibit invasion of cells associated with detrimental healing processes. The materials described, however, are not covalently polymerized, do not have mechanical integrity and do not bind to tissue. Such materials also may interfere with normal wound healing during the postoperative period.

Hydrogels are materials which absorb solvents (such as water), undergo rapid swelling without discernible dissolution, and maintain three-dimensional networks capable of reversible deformation. Because of their high water content and biocompatibility, hydrogels have been proposed for use as barriers for adhesion prevention.

U.S. Patent No. 4,994,277 to Higham et al. describes the use of xanthan gum for preventing adhesions, wherein the hydrogel is more viscous than blood and is soluble in aqueous solutions. The water solubility of that gel system, however, enhances clearing and migration of the barrier. U.S. Patent No. 4,911,926 to Henry et al. describes a method and composition for reducing post-surgical adhesions using aqueous and non-aqueous compositions comprising a polyoxyalkylene block copolymer. The resulting thermoreversible gels are not covalently crosslinked and have no mechanical integrity, thus making the barrier readily susceptible to displacement from the application site. The foregoing materials have shown limited efficacy in clinical trials.

U.S. Patent No. 5,126,141 to Henry describes a composition and method for post-surgical adhesion reduction with thermo-irreversible gels of polyoxyalkylene polymers and ionic polysaccharides. These aqueous gels are rendered thermally irreversible upon contact with a counter-ion. A serious drawback of such systems is the biodegradability and absorbability of such barriers. Because there is no clear mechanism for the degradation of these ionically crosslinked materials, the barriers may remain biostable for uncertain periods of time and adversely impact the patient's health.

A similar disadvantage exists with respect to the barrier system described in U.S. Patent No. 5,266,326 to Barry et al. That patent describes the in situ modification of alginate to form a hydrogel in vivo. Ionically crosslinked polysaccharides such as alginate are not absorbable in humans since no enzyme exists in humans to degrade the β glycosidic linkages. Moreover, the high molecular weight of the alginates used (upwards of 200,000 Da) do not allow filtration through the kidneys. The inability to eventually biodegrade the material is considered a major drawback.

U.S. Patent No. 4,911,926 to Henry et al. describes aqueous and nonaqueous compositions comprised of block polyoxyalkylene copolymers that form gels in the biologic environment to prevent post-surgical adhesion. Other gel forming compositions have been suggested for use in preventing post-surgical adhesion, including: chitin derivatives (U.S. Patent No. 5,093,319 to Henry et al.); chitosan-coagulum (U.S. Patent No. 4,532,134 to Higham et al.); and hyaluronic acid (U.S. Patent No. 4,141,973 to Balazs).

U.S. Patent No. 4,886,787 to de Belder et al. describes a method of preventing adhesion between body tissues by employing a degradable gel of a crosslinked carboxyl-containing polysaccharide. U.S. Patent No. 5,246,698 to Leshchiner et al. describes biocompatible viscoelastic gel slurries formed from a hyaluronan or a derivative thereof. The foregoing crosslinked gels are not formed in situ, but rather formed outside the body and then implanted as flowable gels. While covalent crosslinking of these materials may prolong residence time of the barrier within a body cavity, because the barriers are not formed in situ they do not adhere to the tissues within the body cavity and present a risk of migration.

Covalently crosslinked hydrogels (or aquagels) have been prepared based on crosslinked polymeric chains of methoxy poly(ethylene glycol) monomethacrylate having variable lengths of the polyoxyethylene side chains. Interaction of such hydrogels with blood components has been studied. See, e.g., Nagaoka, et al., in <u>Polymers as Biomaterial</u> (Shalaby et al., Eds.), Plenum Press, p. 381 (1983). A number of aqueous hydrogels have been used in various biomedical applications, such as, for example, soft contact lenses, wound management, and drug delivery. However, methods used in the preparation of these hydrogels, and conversion of these hydrogels to useful articles, are not suitable for forming these materials in situ in contact with living tissues.

U.S. Patent No. 5,462,976 to Matsuda et al. describes photocurable glycosaminoglycan derivatives, crosslinked glycosaminoglycans and the use of such materials for tissue adhesion prevention. These materials, however, require external energy sources for

transformation.

U.S. Patent 5,410,016 to Hubbell et al. describes free radical polymerizable and biodegradable hydrogels that are formed from water soluble macromers. The patent describes the prevention of post-surgical adhesions using a local photopolymerization method, which shares the same disadvantage of requiring an external energy source. The patent also describes materials that are polymerizable by other free radical mechanisms, such as thermal or redox types of initiation.

Although these latter types of polymerization may be effectively exploited for the formation of regional barriers, only local methods for prevention of adhesion are taught in Hubbell et al.. Also, effective concentrations used for the formation of local barriers using the aforementioned materials have been in the 10%-30% macromer concentration range, reflecting the structural integrity required to prevent migration of a locally adherent barrier. Such concentrations of hydrogel are unsuitable for regional barrier formation for several reasons, including:

1. The amount of macromer solution required for a regional barrier formation is in the range of 200 ml - 3000 ml. At a 10-30% concentration the macromer would approach its toxicity limits for human use.

2. The structural integrity of the hydrogels formed at the foregoing concentrations may result in adverse effects similar to those seen from adhesions themselves, for example, due to the mobility restrictions that may result on visceral organs. Thus, formation of regional barriers at such concentrations may lead to postoperative pain and bowel obstructions.

3. Since such hydrogels have been observed to have an equilibrium water content in the range of 2-8%, the additional hydration of a large hydrogel mass in the abdominal or pelvic cavity may constrict and deform organs and tissue and thus have adverse effects. See, e.g., Sawhney et al., "Bioerodible hydrogels based on photopolymerized poly(ethylene glycol)-co-poly(α-hydroxy acid) diacrylate macromers", *Macromolecules*, 26:581-587 (1993).

In view of the foregoing, it would be desirable to provide in situ formation of regional barriers by macromer solutions at concentrations close to the equilibrium hydration levels to reduce or prevent post-surgical adhesion formation.

It further would be desirable to provide methods that enable a surgeon to create a regional barrier with little reliance on skill and accuracy of placement, thereby overcoming some of the significant drawbacks of previously known local adhesion prevention barriers.

Summary Of The Invention

In view of the foregoing, it is an object of this invention to provide methods of preventing post-surgical tissue adhesion that overcome the drawbacks of previously known methods while providing the regional benefits obtained from pharmacological approaches.

It is another object of this invention to provide in situ formation of regional barriers by macromer solutions at concentrations close to equilibrium hydration levels, to reduce or prevent post-surgical adhesion formation.

It is a further object of the present invention to provide methods that enable a surgeon to

create a regional barrier with little reliance on skill and accuracy of placement, thereby overcoming some of the significant drawbacks of previously known local adhesion prevention barriers.

It is yet another object of this invention to provide methods of delivering drugs or other bioactive molecules to organs within a body cavity using a tissue adherent hydrogel layer that has a predictable residence time.

These and other objects of the present invention are accomplished in accordance with the principles of the present invention by providing methods of using hydrogels to form regional barriers in situ to prevent the formation of post-surgical adhesions. The regional hydrogel layers of the present invention also may be used to deliver drugs or other therapeutic agents to the region of interest, typically a body cavity.

Several methods for the formation of regional adhesion barriers are described, in which any of a variety of water soluble macromeric precursors are used. The term "macromeric precursor" or "macromer" is meant to connote an oligomeric or polymeric molecule that contains functional groups that enable further polymerization. Preferably the functionality of a macromer molecule is >1 so that a crosslinked network or hydrogel results upon polymerization. Hydrogels that resorb or degrade over a period of time are preferred, and more preferably, those that resorb within one or a few months.

In a preferred method, a crosslinked regional barrier is formed in situ, for example, by free radical polymerization initiated by a redox system or thermal initiation, wherein two components of an initiating

system are simultaneously, sequentially or separately instilled in a body cavity to obtain widespread dispersal and coating of all or most visceral organs within that cavity prior to gelation and crosslinking of the regional barrier. Once the barrier is formed, the organs remain isolated from each other for a predetermined period, depending upon the absorption profile of the adhesion barrier material.

Preferably, the barrier does not undergo significant hydration, and is selected to have a low stress at break in tension or torsion, so as to not adversely affect normal physiological function of visceral organs within the region of application. The barrier also may contain a drug or other therapeutic agent.

Detailed Description Of The Invention

Preferred macromers suitable for practicing the methods of the present invention include water soluble crosslinkable polymeric monomers that have a functionality >1 (i.e., that form crosslinked networks on polymerization) and that form biodegradable hydrogels. The in situ formed hydrogels of the present invention may be crosslinked using several types of initiating systems. Some of these initiating systems require an external energy source, for example, in the form of radiation, focused ultrasound, or other means. Photopolymerization using ultraviolet or visible radiation has been widely used to polymerize free radically crosslinkable materials.

Within an animal or human body, at the sites of localized disease, it is useful to control the polymerization process to reduce or prevent post-surgical adhesion. The location of post-surgical adhesion formation, however, often is not predictable,

and occurs not at the site of iatrogenic intervention. Instead, the location of adhesions depends on many factors, including pre-existing disease, ischemia, etc.

In accordance with the present invention, methods are provided that permit diffuse coating of wide and complicated tissue geometries to form "regional" barriers, by coating essentially all tissues in the region of intervention with an adherent crosslinked hydrogel barrier.

The process of the present invention is conceptually similar to "hydroflotation," which entails filling up a body cavity with a lubricious fluid to float the organs within the cavity in isolation of each other. In hydroflotation, the fluid is invariably rapidly absorbed and cleared, leading promptly to organ apposition and adhesion formation.

In accordance with the principles of the present invention, an in situ formed hydrogel is used to "float" the organs for substantially longer than is possible with hydroflotation methods. Whereas hydroflotation has been associated with fluidic imbalances in the patient resulting from the use of hyperosmolar fluids, the method of the present invention does not rely on osmolality. Instead, it is the crosslinked structure of the hydrogel that prolongs residence of the barrier within the body cavity. Thus, the precursor solutions and the resulting hydrogel barrier may be iso-osmolar with the surrounding physiological fluids, and do not create any fluidic imbalances.

For macromers that possess ethylenically unsaturated bonds, regional barriers may be formed for example, by a free radically initiated polymerization. This may be undertaken using chemically (such as a

redox system) and thermally activated initiating systems. Photopolymerization processes may optionally be used, but such processes typically are better suited for a local polymerization approach as opposed to a regional one. This is so because some tissues and organs may not transmit light of the wavelength being used. Also, photopolymerization generally is restricted to a "spot-by-spot" approach, and is unsuitable when it may be difficult to predict where the adhesions are likely to originate.

Other means for polymerization of macromers to form regional barriers may also be advantageously used with macromers that contain groups that demonstrate activity towards functional groups such as amines, imines, thiols, carboxyls, isocyanates, urethanes, amides, thiocyanates, hydroxyls etc. that may either be naturally present in, on, or around tissue or may be optionally provided in the region as part of the instilled formulation required to effect the barrier.

Materials Suitable for
Formation of Regional Barriers

Absorbable polymers, often referred to as biodegradable polymers, have been used clinically in sutures and allied surgical augmentation devices to eliminate the need for a second surgical procedure to remove functionally equivalent non-absorbable devices. See, e.g., U.S. Patent No. 3,991,766 to Schmitt et al. and Encyclopedia of Pharmaceutical Technology (Boylan & Swarbrick, Eds.), Vol. 1, Dekker, New York, p. 465 (1988). Interest in using such absorbable systems, with or without biologically active components, in medical applications has grown significantly over the past few years. Such applications are disclosed in

Bhatia, et al., *J. Biomater. Sci., Polym. Ed.*, 6(5):435 (1994); U.S. Patent No. 5,198,220 to Damani; U.S. Patent No. 5,171,148 to Wasserman, et. al.; and U.S. Patent No. 3,991,766 to Schmitt et al.

Absorbable hydrogels that may be formed and crosslinked in situ to form a network are preferred materials for practicing the current invention. Synthesis and biomedical and pharmaceutical applications of absorbable or biodegradable hydrogels based on covalently crosslinked networks comprising polypeptide or polyester components as the enzymatically or hydrolytically labile components, respectively, have been described by a number of researchers. See, Jarrett et al., "Bioabsorbable Hydrogel Tissue Barrier: In Situ Gelatin Kinetics," *Trans. Soc. Biomater.*, Vol. XVIII, 182 (1995); Sawhney et al., "Bioerodible hydrogels based on photopolymerized poly(ethylene glycol)-co-poly(α-hydroxy acid) diacrylate macromers", *Macromolecules*, 26:581-587 (1993); Park, et al., Biodegradable Hydrogels for Drug Delivery, Technomic Pub. Co., Lancaster, PA., 1993; Park, "Enzyme-digestible swelling hydrogels as platforms for long-term oral drug delivery: synthesis and characterization," *Biomaterials*, 9:435-441 (1988).

Hydrogels described in the literature include, for example, those made of water-soluble polymers, such as polyvinyl pyrrolidone, which have been crosslinked with naturally derived biodegradable components such as those based on albumin.

Totally synthetic hydrogels are based on covalent networks formed by the addition polymerization of acrylic-terminated, water-soluble chains of polyether-poly(α-hydroxyester) block copolymers. These

materials are among those preferred for practicing the present invention because they have been used for in vivo applications and have been demonstrated to be biocompatible. Details of compositions and methods to synthesize such materials have been described in U.S. Patent No. 5,410,016 to Hubbell et al., which is incorporated herein by reference.

Preferred macromers for use in forming regional barriers for prevention of adhesion in accordance with the principles of the present invention include any of a variety of in situ polymerizable macromers that form hydrogel compositions absorbable in vivo. These macromers, for example, may be selected from compositions that are biodegradable, polymerizable, and substantially water soluble macromers comprising at least one water soluble region, at least one degradable region, and statistically more than 1 polymerizable region on average per macromer chain, wherein the polymerizable regions are separated from each other by at least one degradable region. The individual regions that comprise such macromers are described in detail below.

<u>Water Soluble Regions</u>

The water soluble region is selected from any of a variety of natural, synthetic, or hybrid polymers the group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(allyl alcohol), poly(vinylpyrrolidone), poly(ethyleneimine), poly(allylamine), poly(vinyl amine), poly(aminoacids), poly(ethyloxazoline), poly(ethylene oxide)-co-poly(propyleneoxide) block copolymers, polysaccharides, carbohydrates, proteins, and combinations thereof.

Random copolymers of monomers that form water soluble polymers also may be used, for example,

copolymers of vinyl amine and allyl alcohol. These types of random copolymers are preferred when the crosslinking reaction is mediated by nucleophilic or electrophilic functional groups. The water soluble region also may be selected from species that are capable of being rendered hydrophilic in a post-polymer reaction. For example, vinyl esters of carboxylic acids such as vinyl formate, vinyl acetate, vinyl monochloroacetate, and vinyl butyrate, may be copolymerized with the afore-described copolymerizable macromolecular monomers. Subsequent to the copolymerization reaction, the polymeric backbone (containing repeating monomeric units of these vinyl esters of carboxylic acids) may be rendered hydrophilic by hydrolysis to the resulting polyvinyl alcohol. In other words, the polymeric backbone comprises a polyvinyl alcohol.

Suitable species that may be polymerized and used in preparing the hydrophilic polymeric backbone of the macromers useful in the present invention include:

acrylic and methacrylic acid;

water-soluble monoesters of acrylic and methacrylic acid in which the ester moiety contains at least one hydrophilic group such as a hydroxy group, i.e., the hydroxy lower alkyl acrylates and methacrylates, typical examples of which include:

2-hydroxyethyl acrylate,
2-hydroxyethyl methacrylate,
2-hydroxypropyl acrylate,
2-hydroxypropyl methacrylate,
3-hydroxypropyl acrylate,

3-hydroxypropyl methacrylate,
diethylene glycol monomethacrylate,
diethylene glycol monoacrylate,
dipropylene glycol monomethacrylate, and
dipropylene glycol monoacrylate;

water-soluble vinyl monomers having at least one nitrogen atom in the molecule, examples of which include:
acrylamide,
methacrylamide,
methylolacrylamide,
methylolmethacrylamide,
diacetone acrylamide
N-methylacrylamide,
N-ethylacrylamide,
N-hydroxyethyl acrylamide,
N,N-disubstituted acrylamides, such as N,N-dimethylacrylamide, N,N-diethylacrylamide,N-ethylmethylacrylamide, N,N-dimethylolacrylamide, and N,N-dihydroxyethyl acrylamide

heterocyclic nitrogen containing compounds such as N-pyrrolidone, N-vinyl piperidone, N-acryloylpyrriolidone, N-acryloylpiperidine, and N-acryloylmorpholene; and

cationic functional monomers, for example, vinyl pyridene quaternary ammonium salts and dimethyl

aminoethyl methacrylate quaternary ammonium salts.

Suitable hydrophobic copolymerizable monomers also may be interpolymerized with hydrophobic copolymerizable macromolecular monomers and the aforementioned hydrophilic copolymerizable comonomers, so long as the ultimate products of biodegradation are water soluble. Hydrophobic species may include the alkyl acrylates and methacrylates, e.g., methylacrylate or methylmethacrylate, ethylacrylate or ethylmethacrylate, propylacrylate or propylmethacrylate, butylacrylate or butylmethacrylate, butylacrylate being preferred. Other suitable hydrophobic copolymerizable comonomers include vinyl chloride, vinylidene chloride, acrylonitrile, methacrylonitrile, vinylidene cyanide, vinyl acetate, vinyl propionate, and vinyl aromatic compounds such as styrene and alpha-methylstyrene, and maleic anhydride.

Degradable Regions

The degradable region is selected from any of a variety of polymers that undergo either hydrolytic, enzymatic, or thermal decomposition by bond scission of linkages so as to produce ultimately soluble and physiologically cleared molecules. Preferable biodegradable polymers, oliogomers or even single moieties can be selected from the group consisting of poly(α-hydroxy acids), poly(lactones), poly(amino acids), peptide sequences, oligonucleotides, poly(saccharides), poly(anhydrides), poly(orthoesters), poly(phosphazenes), and poly(phosphoesters), poly(urethanes), poly(amides), poly(imines), poly(esters), phosphoester linkages and combinations, copolymers, blends, etc. In some cases the water soluble and the degradable region may be one and the

same, for example, in the case of proteins and poly(saccharides) that are degraded by naturally existing enzymes within the body.

Polymerizable Regions

The polymerizable end groups in these macromers may consist of groups that either react within themselves, with added excipients, or with the surface of tissue to form tissue protective coatings that function as regional barriers. Preferable end groups that mainly react within themselves may be selected from ethyleneically unsaturated functional groups such as acrylate, allyl, vinyl, methacrylate, cinnamate, or other ethylenically unsaturated functional groups.

Polymerizable groups may be selected from nucleophilic groups and their salts that react further, for example, with acylating agents. Useful nucleophilic groups may include primary, secondary, tertiary, or quaternary amino, amide, urethane, urea, hydrazide or thiol groups. These functional groups may be present along the main chain of the water soluble macromer or present only at the end groups. When they are present along the main chain of the macromer, they may be evenly spaced, as in a block copolymer, or they may be randomly spaced.

For example, Shearwater Polymers, Huntsville, AL, sell p-PEGs which contain pendant functional groups. Optionally these groups may be spaced from the polymeric main chain (either at the chain ends or along the backbone) by spacer groups that may contain ester linkages. The preparation of macromers containing amino acid esters of PEG is described, for example, in Zalipsky et al., "Esterification of Polyethylene Glycols," *J. Macromol. Sci. Chem.*, A21:839 (1984). The

presence of such linkages can impart desirable properties such as speed of polymerization and predictable instability of the linkage.

Nucleophilic functional group-containing macromers optionally may be mixed with electrophilic group-containing macromers to rapidly initiate polymerization. It should be noted that several nucleophilic and electrophilic functional groups are naturally present in proteins, polysaccharides, glycosaminoglycans, and oligonucleotides that constitute tissue, cells, and organs and thus both nucleophilic and electrophilic macromers may react with appropriate naturally occurring functional groups in the absence of any additional externally added macromers.

For purposes of the present invention, however, reaction rates are more predictable and the resulting hydrogel will have more predictable properties if both components are added externally so as to initiate polymerization and formation of the hydrogel. Electrophilic groups that may be useful to react with the aforementioned nucleophilic groups may include carboxyl groups that may or may not be separated from the polymeric main chain (either at the chain ends or along the backbone) by spacer groups that may contain ester linkages (for example esters of succinic acid, carboxymethyl esters, esters of propionic, adipic, or amino acids), among others.

Other useful groups include isocyanate, thiocyanate, N-hydroxy succinamide esters such as succinamide as well as succinamide groups that are spaced by groups such as esters or amino acids, among others such as succinimidyl succinates, succinimidyl propionates, succinimidyl succinates, succinimidyl

esters of carboxymethylated water soluble polymers, benzotriazole carbonates, and any of a variety of carbodiimides also may be selected. PEG succinimidyl succinates, PEG succinimidyl propionates, succinimidyl esters of amono acid or carboxymethylated PEG, and PEG succinamidyl succinamides are particularly suitable as electrophilically active macromers that react with nucleophilic group-containing macromers due to their high reactivity at physiological pH and speed of polymerization.

Other useful electrophilic macromers may contain functional groups such as glycidyl ethers (or epoxides) or hydroxyl group containing polymers that have been activated with 1,1,-carbonyl diimidazole (for example PEG-oxycarbonylimidazole) or p-nitrophenyl chlorocarbonates (e.g., PEG nitrophenyl carbonate), tresylates, aldehydes and isocyanates. Other groups reactive towards nucleophilic moieties may include for example anhydrides.

Thus, for example, a polymer of maleic anhydride when copolymerized with allyl or vinyl group containing water soluble polymers (such that the vinyl or allyl or other ethylenically unsaturated functionality is 1 per molecule or lower) forms a water soluble co-polymer that contains anhydride groups along the backbone. These anhydride groups are reactive towards any of the various nucleophilic groups mentioned hereinabove. Other electrophilic groups, that are more selective towards specific nucleophiles (such as sulfahydryl groups), also may be used, such as vinylsulfone, maleimide, orthopyridyl disulfide or iodoacetamide containing macromers.

It is to be understood that more than one type of electrophilic group or nucleophilic group may

be present as a part of a macromer chain, so that multiple levels of reactivities may be built into the materials. In fact, both electrophilic and nucleophilic groups may be built into the same molecule and the solution prepared at a pH where the reactivity between these functional groups is low. A second solution that restores the appropriate pH upon mixing then may be added to initiate the crosslinking reaction.

Also, the concentration and number of the functional groups may be varied to obtain different rates of reactivity. The pH of the solutions may be varied to control rates of reaction, and the properties of the resulting crosslinked hydrogel also may be tailored by appropriate selection of the reactive macromers. For example, a higher molecular weight between crosslinks may lead to the formation of a lower modulus and more flexible hydrogel.

<u>Delivery of Bioactive Species</u>

The regional barriers of the present invention further may have bioactive molecules either dissolved or dispersed within them. The dispersed or dissolved drugs may be present as a particulate suspension, that either may or may not further be contained in a secondary containment membrane or coating, microspheres, or microcapsule. The materials for such secondary coating and containment also may be selected from any of a variety of biodegradable natural or synthetic hydrophobic materials that provide resistance to diffusion of small molecules, especially water soluble small molecules.

The biologically active molecules may include proteins (including growth factors and enzymes that may demonstrate bioactivity), carbohydrates, nucleic acids

(both sense and antisense as well as gene fragments for gene therapy), organic molecules, inorganic biologically active molecules, cells, tissues, and tissue aggregates. Biologically active molecules may include any of the beneficial drugs as are known in the art, and described, for example, in Pharmaceutical Sciences, by Remington, 14th Ed., 1979, published by Mack Publishing Co.; The Drug, The Nurse, The Patient, Including Current Drug Handbook, by Falconer et al., 1974-1976, published by Saunder Company; and Medicinal Chemistry, 3rd Ed., Vol. 1 and 2, by Burger, published by Wiley-Interscience Co.

The drugs selected may serve to act against an underlying pathological condition that is suspected to contribute to the formation of adhesions, such as drugs that interfere with the polymerization of fibrin, serve as anticoagulants (such as heparin, hirudin, etc.) or act to dissolve fibrin clots or disrupt the native fibrinogen (such as tissue plasminogen activator, urokinase, streptokinase, streptodornase, ancrod, etc). Drugs having an antiinflammatory effect may be used, such as medroxyprogestrone acetate, which has been observed to reduce postoperative adhesion formation in animal studies. Other antiinflammatory compounds such as antibodies to IL-6, IL-1, TNF-α, and TGF-β have demonstrated efficacy as well.

Preferably, the drugs are directed to a process unique to adhesion formation, and which does not disrupt normal healing. For example, pentoxifylline, a drug used to treat intermittent claudication, and calcium channel blockers, such as verapamil, have been shown to reduce postoperative adhesion formation. It is thus expected that the delivery of one or more therapeutic compounds in a

hydrogel-based regional barrier capable of controlled release may further enhance the prevention of postoperative adhesions. Thus, drugs that may be advantageously delivered using the regional barrier of the present invention include antiinflammatory compounds, antifibrinolytics, targeted modulators that interfere with the pathways of adhesion formation, such as IL-10 and antibodies to various cytokines, and immunomodulators.

Drugs delivered by the regional barrier also may serve to supplement the overall therapeutic regimen for the particular patient by delivering a drug or a combination of drugs that address another disease state. For example, physiologically active materials or medicinal drugs, such as agents affecting the central nervous system, antiallergic agents, cardiovascular agents, agents affecting respiratory organs, agents affecting digestive organs, hormone preparations, agents affecting metabolism, antitumor agents, antibiotic preparations, chemotherapeutics, antimicrobials, local anesthetics, antihistaminics, antiphlogistics, astringents, vitamins, antifungal agents, peripheral nervous anesthetics, vasodilators, crude drug essences, tinctures, crude drug powders, immunosuppressants, hypotensive agents, and the like may be delivered.

Drugs that are delivered using the regional barriers of the present invention may include both water soluble as well as partially water soluble or even lipophilic drugs. The drugs may be small molecules or macromolecular in nature. Particular water-soluble polypeptides which may be used in this invention are, for example, oxytocin, vasopressin, tissue plasminogen activator, urokinase, and other

fibrinolytic enzymes, adrenocorticotrophic hormone (ACTH), epidermal growth factor (EGF), transforming growth factor antagonists, prolactin, luliberin or luteinizing hormone releasing hormone (LH-RH), LH-RH agonists or antagonists, growth hormone, growth hormone releasing factor, insulin, somatostatin, bombesin antagonists, glucagon, interferon, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endomorphins, angiotensins, renin, bradykinin, bacitracins, polymyzins, colistins, tyrocidin, gramicidines, and synthetic analogues and modifications and pharmaceutically-active fragments thereof, monoclonal antibodies and soluble vaccines.

The water-soluble drugs that may be delivered by this method are not specifically limited. Examples include peptides having biological activities, other antibiotics, antitumor agents, antipyretics, analgesics, anti-inflammatory agents, antitussive expectorants, sedatives, muscle relaxants, antiepileptic agents, antiulcer agents, antidepressants, antiallergic agents, cardiotonics, antiarrhythmic agents, vasodilators, hypotensive diuretics, antidiabetic agents, anticoagulants, hemostatics, antituberculous agents, hormone preparations, narcotic antagonists, bone resorption inhibitors, angiogenesis inhibitors and the like.

Examples of antitumor agents include bleomycin hydrochloride, methotrexate, actinomycin D, mitomycin C, vinblastine sulfate, vincristine sulfate, daunorubicin hydrochloride, adriamycin, neocarzinoszatin, cytosine arabinoside, fluorouracil, tetrahydrofuryl-5-fluorouracil krestin, picibanil, lentinan, levamisole, bestatin, azimexon, glycyrrhizin, poly I:C, poly A:U, poly ICLC, cisplatin and the like.

The terms "cytokine" and "growth factor" are used to describe biologically active molecules and active peptides (which may be either naturally occurring or synthetic) that aid in healing or regrowth of normal tissue, including growth factors and active peptides. The function of cytokines is two-fold: (1) to incite local cells to produce new collagen or tissue, or (2) to attract cells to a site in need of correction. For example, one may incorporate cytokines such as interferons (IFN), tumor necrosis factors (TNF), interleukins, colony stimulating factors (CSFs), or growth factors such as osteogenic factor extract (OFE), epidermal growth factor (EGF), transforming growth factor (TGF) alpha, TGF-β (including any combination of TGF-βs), TGF-β1, TGF-β2, platelet derived growth factor (PDGF-AA, PDGF-AB, PDGF-BB), acidic fibroblast growth factor (FGF), basic FGF, connective tissue activating peptides (CTAP), β-thromboglobulin, insulin-like growth factors, erythropoietin (EPO), nerve growth factor (NGF), bone morphogenic protein (BMP), osteogenic factors, and the like.

Suitable biologically-active agents for use in the present invention also include oxygen radical scavenging agents such as superoxide dismutase or anti-inflammatory agents such as hydrocortisone, prednisone and the like; antibacterial agents such as penicillin, cephalosporins, bacitracin and the like; antiparasitic agents such as quinacrine, chloroquine and the like; antifungal agents such as nystatin, gentamicin, and the like; antiviral agents such as acyclovir, ribavirin, interferons and the like; antineoplastic agents such as methotrexate, 5-fluorouracil, adriamycin, taxol, taxotere, tumor-specific antibodies conjugated to

toxins, tumor necrosis factor, and the like; analgesic agents such as salicylic acid, acetaminophen, ibuprofen, flurbiprofen, morphine and the like; local anesthetics such as lidocaine, bupivacaine, benzocaine and the like; vaccines such as hepatitis, influenza, measles, rubella, tetanus, polio, rabies and the like; central nervous system agents such as a tranquilizer, β-adrenergic blocking agent, dopamine and the like; growth factors such as colony stimulating factor, platelet-derived growth factors, fibroblast growth factor, transforming growth factor B, human growth hormone, bone morphogenetic protein, insulin-like growth factor and the like; hormones such as progesterone, follicle stimulating hormone, insulin, somatotropins and the like; antihistamines such as diphenhydramine, chlorphencramine and the like; cardiovascular agents such as digitalis, nitroglycerine, papaverine, streptokinase and the like; vasodilators such as theophylline, niacin, minoxidil, and the like; and other like substances.

The regional hydrogel barriers also may be used to delivery antitumor, antineoplastic, or anticancer agents to the body cavity, wherein multiple tumor sites exist and it may not be possible to accurately identify all sites of disease.

Physical and Mechanical Characteristics of Materials Suitable for Formation of Regional Barriers

Materials suitable for use in forming the regional barriers in accordance with the present invention preferably have certain physical and mechanical attributes. These include safety, effectiveness at adhesion prevention, absorbability, non-inflammatoriness, compatibility with laparoscopic use, ease of use, efficacy at sites distant to surgery,

lack of interference with normal healing, suitability as a pharmaceutical carrier, and conformity to tissue. While no adhesion barrier material may possess all of these properties, the materials described hereinabove satisfy many of these criteria.

In addition to the foregoing criteria, crosslinked materials suitable for use as regional tissue adherent adhesion barriers or drug delivery systems in accordance with the present invention should exhibit the following characteristics: (1) the materials should not obstruct the normal functioning of internal organs; and (2) these materials should not cause a substantial hydraulic imbalance after instillation and polymerization.

The first requirement ensures that, despite the extensive regional presence of the barrier throughout a body cavity, it will not impede normal tissue movement. Thus, even though the hydrogel barrier is crosslinked, it should not have the structural strength to adhere or bind organs together tenaciously. It is instead preferable that the barrier have weak cohesive strength and fail within the bulk of the material, rather than constrict organs to which it is applied. Desirable materials are expected to have stress at shear or tensile loading failure of less than 1 MPa. More preferably, the stress at failure should be between less than 300 KPa, and more preferably, less than 100 KPa.

The regional barriers need not form bulk hydrogels, but may form coatings on tissue upon instillation that may be thin and of the order of 1-1000 microns in thickness. In fact, the coating even may be formed as a surface modification of the tissue by instillation of macromers that have a reactivity to

functional groups found on the surface of the tissues at risk for formation of adhesions. The instillation of the precursor solutions may be simultaneous or sequential, with a first solution coating tissue for some period of time and the subsequent solution being administered just prior to completion of the surgical procedure and closure of the surgical access points or incision.

The quantity of water contained within a hydrogel may be evaluated as "% Water Content," defined as:

$$\text{\% Water Content} = 100 * \frac{(\text{Wet Hydrogel} - \text{Dry Hydrogel})}{\text{Wet Hydrogel}}$$

where:

Wet Hydrogel - the weight of wet hydrogel; and

Dry Hydrogel - the weight of dry hydrogel.

Hydrogels continue to absorb water from surrounding aqueous fluids until they reach an equilibrium level of hydration. During this process the addition increase in water content can be determined by measuring the % Hydration, which is defined as:

$$\text{\% Hydration} = 100 * \frac{(\text{Wt. Hydrogel}_{Eq} - \text{Wt. Hydrogel}_{F})}{\text{Wt. Hydrogel}_{F}}$$

where:

Wt. Hydrogel_{Eq} - the weight of hydrogel at equilibrium; and

Wt. Hydrogel_{F} - the weight of hydrogel at formation.

The requirement that the barrier material not create a hydraulic imbalance in situ arises from the relatively large volumes of such materials that are needed to form regional barriers as opposed to local barriers. It is expected, for example, that a typical use of regional barrier material in accordance with the present invention will involve the instillation of precursor materials in excess of 200 ml, possibly in excess of 500 ml, and in some cases, even as high as 3000 ml. Due to such relatively large volumes of instillates, it is important that the resulting regional barrier be relatively isotonic and near equilibrium hydration, i.e. it will not continue to absorb fluid from within the body cavity and induce fluid imbalance in the patient.

Similarly, the materials used to form the regional barriers of the present invention also should be close to the equilibrium level of hydration. Thus, the barrier will not appreciably increase in size by hydrating substantially after formation and thus will not impose undesirable mechanical obstructions within the body cavity. Accordingly, materials that hydrate less than 100% beyond their own weight in physiological aqueous solutions, at time of formation, are preferred. More preferable are materials that hydrate less than 50% of their own weight, and more preferably, materials that hydrate less than 20% beyond their initial weight at time of formation.

It is to be understood, based upon the foregoing discussion, that materials suitable for practicing the present invention should have many of the other beneficial properties expected of adhesion barrier materials, such as not eliciting an inflammatory response. If the barrier material

generates a significant inflammation, it may enhance the formation of adhesions, rather than reducing or eliminating them. For example talc, which is considered to be an inflammatory material, is often used to create adhesions within the chest cavity by a regional instillation.

The hydrogel barriers formed in accordance with the methods of the present invention preferably are absorbed over time by natural physiological processes, so that the organs within the region of interest ultimately return to their original conformations. Absorption of the barrier material is defined herein as a lack of physical evidence of presence of the barrier at the application site. Preferably, the regional barriers of the present invention should absorb within 6 months, more preferably within 2 months, and most preferably within 1 month.

<u>Free radical Initiating Systems</u>

Many previously known chemical systems that use free radical polymerization do not depend on external energy sources such as photoexcitation. Such systems advantageously may be used at physiological conditions of temperature and do not create physiologically toxic effects at the concentrations used. For example, Roland et al., "Recent Developments in Free-Radical Polymerization-A Mini Review," *Progress in Organic Coatings*, 21:227-254 (1992), presents an overview of the free radical polymerization process, with an emphasis on recent developments.

U.S. Patent No. 4,511,478 to Nowinski et al. describes several types of oxidation-reduction initiators, including: (1) peroxides in combination

with a reducing agent, e.g., hydrogen peroxide with ferrous ion or other transition metal ions, or benzoyl peroxide with an N,N-dialkylaniline or toluidine, and (2) persulfates in combination with a reducing agent, such as sodium metabisulfite or sodium thioslfate.

Specifically, ammonium persulfate, benzoyl peroxide, lauryl peroxide, tert-butyl hydroperoxide, tert-butyl perbenzoate, cumene hydroperoxide, dibenzoyl peroxide, tert-butyl peroctoate, tert-butyl peracetate, di-tert-amyl peroxide, di-tert-butyl peroxide, tert-amyl perpivalate, butyl per-2-ethyl-hexanoate, tert-butyl perpivalate, tert-butyl perneodecanoate, tert-butyl perisononanoate, tert-amylperneodecanoate, di-2-ethyl-hexyl peroxydicarbonate, dicyclohexyl peroxydicarbonate, cumyl perneodecanoate, tert-butyl permaleate, 1,3-bis-(t-butylperoxyisopropyl)benzene, succinic acid peroxide, bis(1-hydroxycyclohexyl)-peroxide, isopropyl percarbonate, methyl ethyl ketone peroxide, and dicumyl peroxide, potassium ferricyanide, potassium permanganate, ceric sulfate, pinane hydroperoxide, di-isopropylbenzene hydroperoxide and other oxidizing compounds including combinations thereof with reducing agents, such as transition metal ions, sodium hyposulfite, sodium metabisulfite, sodium sulfide, sodium thiosulfate, hydrazine hydrate, sodium bisulfite or sodium thiosulfate, may be used. Sodium bisulfite alone may be used for polymerization.

Other initiators suitable for use in accordance with the methods of the present invention include, but are not limited to azo initiators. Preferred thermally active free radical polymerization initiators for use in the present invention may include, but are not limited to, diazodiisobutyrodinitrile, 2,2'-azobis-

(isobutyronitrile), 2,2'-azobis(2,4-dimethylvaleronitrile), 2,2'-azobis(cyclohexanenitrile), 2,2'-azobis-(2-methylbutyronitrile), 2,2'-azobis(2,4-dimethyl 4-methoxyvaleronitrile), mixtures thereof and several like azo initiators such as those sold by Wako Chemical Co., Richmond, VA. Mixtures of two or more initiators also may be used, if desired.

Another group of catalysts, useful mainly for low temperature polymerization, include redox systems such as potassium persulfate-riboflavin, potassium persulfate-sodium bisulfite. Various compounds such as N,N,N',N-tetramethylethylenediamine and dimethyl toluidine may be used to accelerate the effect of the catalysts. Other suitable catalyst(s) and accelerant(s) may be used to catalyze the polymerization.

Inhibitors of Free Radical Polymerization

Free radical-inhibitors are generally used in the production, transportation and/or storage of systems that are reactive via free radicals to definitely exclude that the system will undergo premature reaction. With respect to the foregoing polymerizable materials, the addition of numerous compounds and/or systems that function as free radical-inhibitors are known, including, for example, hydrides such as lithium aluminum hydride, calcium hydride or sodium borohydride.

Further known examples serving this purpose are phenols, phenol derivatives, hydroquinone and hydroquinone derivatives or, especially, phenothiazine. As typical examples there may be mentioned cumene, hydroquinone, 2,6-di-tert-butyl-p-cresol, BHT, BHA, anisole, 2,6-di-tert-butyl-4-methoxyphenol, bis(2-hydroxy-3-tert-butyl-5-methylphenyl)methane, bis(3,5-

di-tert-butyl-4-hydroxyphenyl)methane, bis(2-hydroxy-3-tert-butyl-5-methylphenyl)sulfide, bis(3-tert-butyl-4-hydroxy-5-methyl-phenyl)sulfide, or also amines such as diphenylamine, N,N'-diphenyl-p-phenylene diamine, 2-phenylbenzimidazole, aniline, dinitrobenzene, 2-nitro-α-naphthol, tetraphenylethylene, triphenylmethane and vitamin E.

Methods of Instillation

In accordance with the methods of the present invention, macromer solutions used in forming regional barriers may be instilled by pouring, spraying (e.g., using two or more spray nozzles that simultaneously spray more than one solution into the region of interest), or by devices such as infusion catheters (e.g., dual lumen catheters or nozzles with mixing tips), funnel like devices, syringes, or bellows like devices with either dual chambers with a distal mixing tip, which is optionally attached, or with two separate devices that are either simultaneously or sequentially employed, etc.

The solutions may be selected so as to have active ingredients separated in two or more solutions that enable the polymerization upon mixing or on contact. Thus, for example, elements of a redox initiating system may be present in separate macromer solutions that either may be used simultaneously, sequentially or separately after an intervening interval of time to effect polymerization. In order to provide control of hydrogel formation, the barriers of the present invention may also include colored indicator substances such as phenol red (0.04-0.008%), thymol blue (0.04-0.1%), furoxone (0.02-0.4%), rivanol (0.45-0.75%) or picric acid (0.01-0.03%); or antibiotics such as tetracycline (0.7-0.17%),

mithramycin (0.1-0.4%), or chlortetracycline (0.1-0.4%). (All percentages are w/v.)

As a result, a color change, such as a green color, will be observed after mixing or penetration of these colored substances (e.g., one is blue, other is yellow). The color changes also may be usefully observed as a result of pH change when two macromeric solution streams that are instilled into the body cavity are mixed, such macromeric solutions being selected such that the crosslinking reaction only occurs when an appropriate pH is reached, which is indicated by the presence of the pH sensitive colorimetric indicator.

Colored species also may be generated as part of the in situ reaction process. For example, the use of p-nitrophenyl activated PEG as a crosslinking molecule with a poly(amine) such as poly(ethyleneimine) will result in the generation of a yellow color due to the formation of p-nitrophenol as a reaction byproduct. This attribute of color appearance may be used to monitor successful deployment of the regional adhesion barrier.

The macromer solutions will typically be used at the end of the particular surgical procedure but may also be used during or even before undertaking the particular surgical procedure so as to serve as tissue protectants during the surgical procedure by hydrating and lubricating such tissues during the surgery. If thermal initiating systems are used, premature polymerization may be prevented by maintaining the solutions at low temperature so that polymerization occurs when physiological temperatures are attained upon instillation.

EXAMPLES

Example 1

A macromer is synthesized as described in U.S. Patent 5,410,016 to Hubbell et al. The macromer may be an acrylated copolymer of poly(ethylene glycol) (M.W. 20,000) and dl-lactide (3-5 equivalents). The material is dissolved in water to form a solution that is 5% w/w, and the solution is divided into two parts. To part A is added enough hydrogen peroxide to give a 150 ppm concentration of H_2O_2. To part B is added enough of a ferrous gluconate salt to achieve a concentration of 3000 ppm. It may be verified that on mixing approximately equal parts of these two solutions, a flexible hydrogel is formed within 10 seconds of pouring into a mold, in the absence of activation by any external energy source.

Example 2

To assess the efficacy of the regional adhesion barrier of Example 1, the following experiment may be conducted. Twelve Sprague Dawley male rats having an average weight of 250 g are divided into two groups of 6 for treatment and control, respectively. The abdomen is shaved and prepared with a betadine solution. A midline incision is made under anesthesia. The cecum is located and 4 to 5 scrapes made on a region about 2 x 1 cm on one side of the cecum, using a 4 x 4 in gauze pad to produce serosal injury and punctuate bleeding. Other abdominal organs also may be allowed to desiccate for 10 minutes during this period. The abdominal incisions in these animals are closed using a continuous 4-0 silk suture for the musculoperitoneal layer and 7.5 mm stainless steel staples for the cutaneous layer. A topical antibiotic

then is applied at the incision site.

The first group consists of 6 animals serving as controls without treatment, to confirm the validity of the model. The second group of 6 animals serves as a treatment with the application of the regional barrier. Approximately 5 cc of solution A described in Example 1 is applied to the injury site and over all the abdominal organs using a pipet. Care should be taken to ensure complete application to all organs. The muscular layer of the abdominal incision then is closed as above until the final suture tie is ready to be placed. At this time 5 cc of solution B from Example 1 above is instilled into the abdominal cavity. The walls of the abdominal cavity should be briefly massaged to ensure dispersal of the solutions and the closure of the abdominal and skin layers completed.

Three of the 6 animals in each group are sacrificed at the end of two days and 3 of the remaining animals in each group are sacrificed at the end of two weeks by CO_2 asphyxiation. The incisions are reopened and gross observations recorded. If adhesions are present, they should be scored for location, extent, and tenacity. The extent of adhesions should be reported as a percentage of the traumatized area of the cecum which forms adhesions with adnexal organs or the peritoneal wall. Tenacity of the adhesions is scored on a scale from 0 to 4: no adhesions - grade 0; tentative transparent adhesions which frequently separate on their own - grade 1; adhesions that give some resistance but can be separated by hand - grade 2; adhesions that require blunt instrument dissection to separate - grade 3; and dense thick adhesions which require sharp instrument dissection in the plane of the adhesion to separate - grade 4. It is expected that in the presence

of the regional adhesion barrier, significant reduction in the extent of adhesion formation will occur.

* * *

Modifications and variations of the present invention, the macromers and polymeric compositions and methods of use thereof, will be obvious to those skilled in the art from the foregoing detailed description. Accordingly, various changes and modifications may be made therein without departing from the invention, and the appended claims are intended to cover all such changes and modifications that fall within the true spirit and scope of the invention.

Claims

<u>What Is Claimed Is:</u>

1. A method of forming a regional barrier to reduce adhesion of tissue to internal structures in a body cavity following surgery:

providing a pharmaceutically acceptable hydrogel system comprising first and second components;

instilling the first component within the body cavity to coat the internal structures;

instilling the second component within the body cavity to coat the internal structures; and

polymerizing at least the first component in situ to form a tissue adherent hydrogel that coats the internal structures to reduce adhesion of tissue to the internal structures.

2. The method of claim 1 wherein polymerizing at least the first component comprises mixing the first and second components.

3. The method of claim 1 wherein instilling the first and second components comprises instilling the first and second components simultaneously.

4. The method of claim 1 wherein instilling the first and second components comprises instilling the first and second components sequentially.

5. The method of claim 4 wherein instilling the first component protects the internal structures during surgery and instilling the second component is performed upon completion of surgery.

6. The method of claim 1 wherein providing a pharmaceutically acceptable hydrogel system comprises providing a first component having at least one water soluble region, at least one degradable region, and at least one polymerizable region.

7. The method of claim 2 wherein each of the first and second components includes a polymerizable region, and crosslinking the first and second components comprises polymerizing the first and second components so that polymerizable regions of the first and second components react.

8. The method of claim 2 wherein polymerizing at least the first component comprises polymerizing the first component by a mechanism selected from a group consisting of: a free radical mechanism, and an electrophilic-neutrophilic mechanism.

9. The method of claim 1 wherein polymerizing at least the first component comprises polymerizing the first component to form a tissue adherent hydrogel at a substantially equilibrium hydration level.

10. The method of claim 1 wherein polymerizing at least the first component comprises polymerizing the first component to form a tissue adherent hydrogel that is substantially isotonic.

11. The method of claim 1 wherein polymerizing at least the first component comprises polymerizing the first component to form a tissue adherent hydrogel having a tensile strength less than 1 MPa.

12. The method of claim 1 further comprising biodegrading the tissue adherent hydrogel within a predetermined period of time.

13. The method of claim 12 wherein biodegrading the tissue adherent hydrogel within a predetermined period of time comprises biodegrading the tissue adherent hydrogel within one month.

14. The method of claim 1 wherein providing a pharmaceutically acceptable hydrogel system comprises providing a pharmaceutically acceptable hydrogel system wherein at least one of the first and second components contains a bioactive molecule that provides a therapeutic benefit.

15. The method of claim 14 wherein providing a pharmaceutically acceptable hydrogel system wherein at least one of the first and second components contains a bioactive molecule comprises providing a pharmaceutically acceptable hydrogel system wherein at least one of the first and second components contains a drug selected from the group consisting of small molecules, macromolecules, proteins, peptides, oligonucleotides, carbohydrates and proteoglycans.

16. The method of claim 14 wherein providing a pharmaceutically acceptable hydrogel system wherein at least one of the first and second components contains a bioactive molecule comprises providing a pharmaceutically acceptable hydrogel system wherein at least one of the first and second components contains a drug selected from the group consisting of drugs that interfere with the process of adhesion formation and drugs that are used to

treat inflammation, cancer and endometriosis.

17. The method of claim 1 wherein the first component contains a color indicator, the method further comprising changing the color indicator responsive to a degree of mixing of the first and second components.

18. A method of delivering bioactive molecules to internal structures in a body cavity following surgery:

providing a pharmaceutically acceptable hydrogel system comprising first and second components, at least one of the first and second components containing a bioactive molecule that provides a therapeutic benefit;

instilling the first component within the body cavity to coat the internal structures;

instilling the second component within the body cavity to coat the internal structures; and

polymerizing at least the first component in situ to form a tissue adherent hydrogel that coats the internal structures.

19. The method of claim 18 wherein polymerizing at least the first component comprises mixing the first and second components.

20. The method of claim 18 wherein instilling the first and second components comprises instilling the first and second components simultaneously.

21. The method of claim 18 wherein instilling the first and second components comprises instilling the first and second components sequentially.

22. The method of claim 21 wherein instilling the first component protects the internal structures during surgery and instilling the second component is performed upon completion of surgery.

23. The method of claim 18 wherein providing a pharmaceutically acceptable hydrogel system comprises providing a first component including at least one water soluble region, at least one degradable region, and at least one polymerizable region.

24. The method of claim 23 wherein each of the first and second components includes a polymerizable region, and polymerizing the first and second components comprises polymerizing the first and second components so that polymerizable regions of the first and second components interact.

25. The method of claim 18 wherein polymerizing at least the first component comprises polymerizing the first component by a mechanism selected from the group consisting of: a free radical mechanism, and an electrophilic-neutrophilic mechanism.

26. The method of claim 18 wherein polymerizing at least the first component comprises polymerizing the first component to form a tissue adherent hydrogel at a substantially equilibrium hydration level.

27. The method of claim 18 wherein polymerizing at least the first component comprises polymerizing the first component to form a tissue adherent hydrogel that is substantially isotonic.

28. The method of claim 18 wherein polymerizing at least the first component comprises polymerizing the first component to form a tissue adherent hydrogel having a tensile strength less than 1 MPa.

29. The method of claim 18 further comprising biodegrading the tissue adherent hydrogel within a predetermined period of time.

30. The method of claim 18 wherein the first component contains a color indicator, the method further comprising changing the color indicator responsive to a degree of mixing of the first and second components.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18522

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/00
US CL :424/484

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/484

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,140,016 A (GOLDBERG et al) 18 August 1992, entire document.	1-30

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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INCEPT LLC [/]; (). SAWHNEY, Amarpreet, S. [/]; (). CAMPBELL, Patrick, K. [/]; (). MELANSON, David, A. [/]; (). JACKSON, Robert, R. ; ().

(54) Title: METHODS AND APPARATUS FOR IN SITU FORMATION OF HYDROGELS
(54) Titre: PROCEDES ET APPAREIL SERVANT A FORMER DES HYDROGELS IN SITU

(57) Abstract

Methods, and apparatus of forming in situ tissue adherent barriers are provided using a sprayer (90) capable of applying two or more viscous cross linking solutions to tissue. The sprayer (90) comprises separate spray nozzles (98, 100) for each of two or more cross linking solutions, wherein each nozzle (98, 100) is in communication with a gas pressurized chamber (48) also may include valves (52) that prevent back flow through the supply lines (99, 101) carrying the cross linking solutions, and a venting system (106, 108) for venting excess pressure for laparoscopic applications. In the presence of gas flow, the cross linking solutions are atomized, and mixed to form a spray. Multi-component hydrogel systems suitable for use with the inventive methods, and apparatus are also described.

(57) Abrégé

L'invention concerne des procédés et un appareil servant à former in situ des barrières adhérant à un tissu au moyen d'un pulvérisateur (90) capable d'appliquer à un tissu deux ou davantage de solutions de réticulation visqueuses. Le pulvérisateur (90) comporte des buses (98, 100) de pulvérisation séparées pour chacune des solutions de réticulation. Chaque buse (98, 100) est en communication avec une chambre (48) de gaz sous pression, et peut également comporter des soupapes (52) empêchant un flux de retour par les trajets (99, 101) d'alimentation contenant les solutions de réticulation, et un système (106, 108) de purge servant à éliminer une pression excédentaire pour des applications de laparoscopie. En présence d'un flux de gaz, les solutions de réticulation sont atomisées, et mélangées pour former une solution pulvérisée. L'invention concerne également des systèmes d'hydrogel à composants multiples pouvant être utilisés avec les procédés de l'invention, et un appareil.

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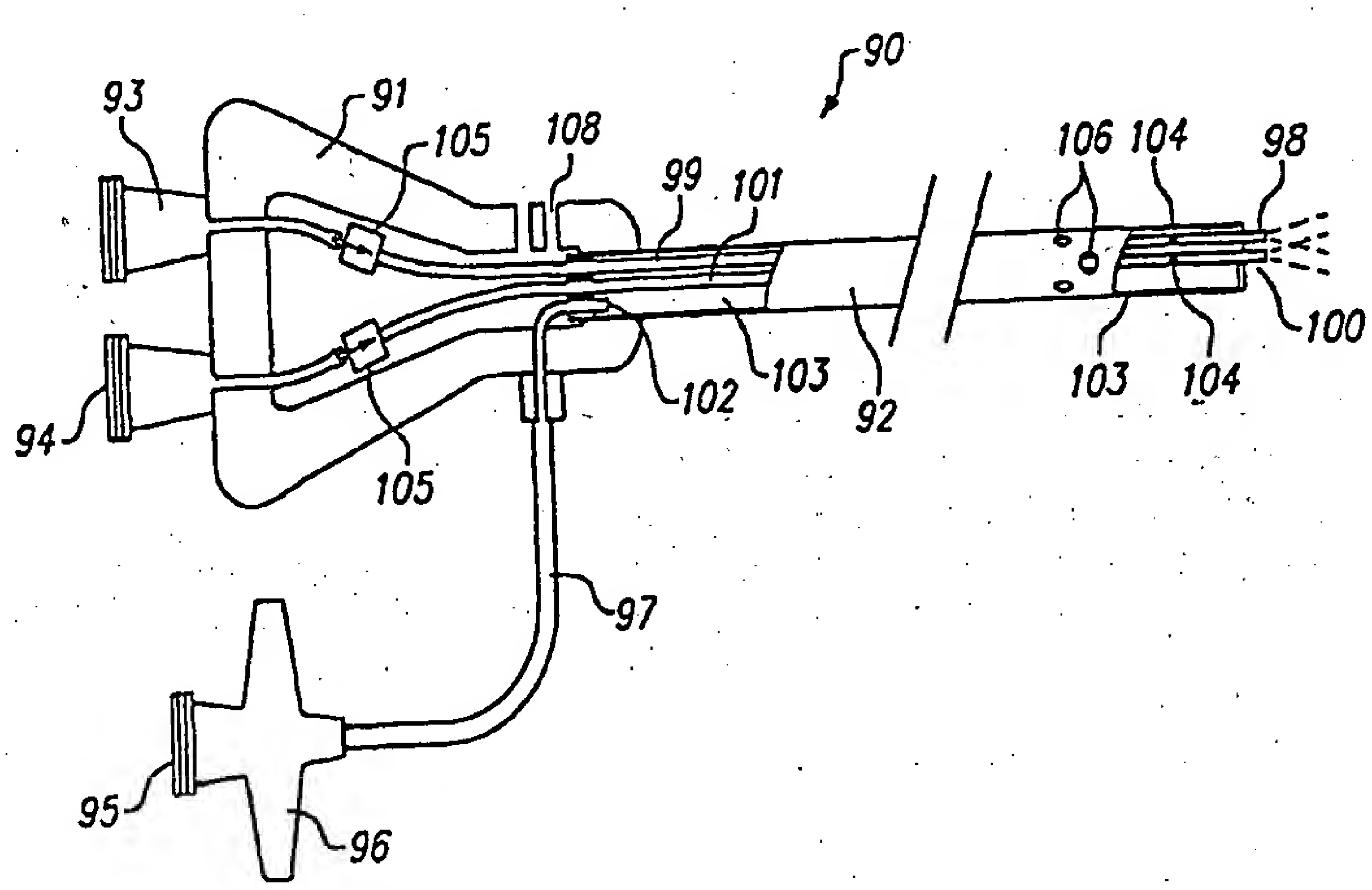

(57) Abstract

Methods, and apparatus of forming in situ tissue adherent barriers are provided using a sprayer (90) capable of applying two or more viscous cross linking solutions to tissue. The sprayer (90) comprises separate spray nozzles (98, 100) for each of two or more cross linking solutions, wherein each nozzle (98, 100) is in communication with a gas pressurized chamber (48) also may include valves (52) that prevent back flow through the supply lines (99, 101) carrying the cross linking solutions, and a venting system (106, 108) for venting excess pressure for laparoscopic applications. In the presence of gas flow, the cross linking solutions are atomized, and mixed to form a spray. Multi-component hydrogel systems suitable for use with the inventive methods, and apparatus are also described.

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Description

METHODS AND APPARATUS FOR IN SITU FORMATION OF HYDROGELS

Field Of The Invention

This present invention relates generally to methods and apparatus for forming hydrogels in situ, especially during minimally invasive surgery. More particularly, the present invention relates to apparatus and methods for delivering two liquid components that form hydrogels upon mixing.

Background Of The Invention

Often during surgery, tissue may be traumatized or compromised such that it needs to be temporarily supported or isolated during the wound healing period. Materials that may be used as tissue sealants also may be used to temporarily support tissue and to seal leaks from tissue until the tissue heals. Tissue sealants that perform these functions are well known in literature and include a variety of natural and synthetic sealants including fibrin sealants, cyanoacrylate based sealants, and other synthetic sealants and polymerizable macromers.

Various types of previously known apparatus have been developed to deliver fibrin sealants, which

are derived from blood-based proteins. For example, U.S. Patent No. 5,605,541 to Holm describes apparatus and methods for applying two or more components of a fibrin sealant. That patent describes a spray head having a central gas discharge port and coaxially arranged annular ports through which respective components of the fibrin sealant are discharged. The spray head may be prone to clogging if the central gas discharge port is restricted.

U.S. Patent No. 5,368,563 to Lonneman et al. describes a sprayer assembly having angular connecting channels through which components of a fibrin sealant are discharged to cause mixing. U.S. Patent 5,341,993 to Haber et al. describes a hand held sprayer having a remotely actuated spray tip. Both of the devices described in those patents may not be suitable for spraying viscous fluids, which tend to emerge as streams rather than as fine sprays.

U.S. Patent No. 4,001,391 to Feinstone et al. describes a method for spraying viscous and buttery fluids using a propellant and a pressurized container. The use of propellants is undesirable in medical applications due to uncertain biocompatibility of these materials.

Applicants further have determined that when attempting to use a propellant to apply materials in a laparoscopic setting, which typically is insufflated with a gas to provide a wider field of view for the clinician, the propellant can result in excessive distension of the tissue surrounding the operative site.

In addition, in the above laparoscopic context, when a sprayer is first introduced into the surgical site, for example, via a trocar tube, the

ambient pressure may inadvertently charge the supply reservoirs (if the supply lines of the sprayer are not already pressurized), thereby interfering with proper dispensing of the materials into the supply lines when the clinician attempts to operate the device.

In view of the foregoing, it would be desirable to provide apparatus and methods that enable a tissue coating comprising two or more crosslinkable fluids to be applied in situ as a spray.

It further would be desirable to provide apparatus and methods for spraying polymerizable fluids with reduced risk of clogging of the sprayer.

It also would be desirable to provide apparatus and methods that permit spraying of polymerizable fluids in a laparoscopic environment, but which adjusts the pressure in the cavity to account for the introduction of propellant from the sprayer, thereby avoiding excessive distension of the tissue surrounding the operative site.

It still further would be desirable to provide apparatus and methods that permit spraying of polymerizable fluids in a laparoscopic environment, but which prevent material reservoirs of the sprayer from being inadvertently pressurized by the backflow of insufflation gases through the supply lines.

<u>Summary Of The Invention</u>

In view of the foregoing, it is an object of the present invention to provide apparatus and methods that enable a tissue coating comprising two or more crosslinkable fluids to be applied in situ as a spray.

It is a further object of this invention to provide apparatus and methods for spraying

crosslinkable fluids with reduced risk of clogging of the sprayer.

It is another object of this invention to provide apparatus and methods that permit spraying of polymerizable fluids in a laparoscopic environment, but which adjusts the pressure in the cavity to account for the introduction of propellant from the sprayer, thereby avoiding excessive distension of the tissue surrounding the operative site.

It is a still further object of the present invention to provide apparatus and methods that permit spraying of polymerizable fluids in a laparoscopic environment, but which prevent material reservoirs of the sprayer from being inadvertently pressurized by the backflow of insufflation gases through the supply lines.

These and other objects of the invention are accomplished by providing a sprayer capable of applying two or more viscous crosslinkable components to tissue to form a coating that adheres to the tissue surface. For example, two crosslinkable solutions, each containing one component of a co-initiating system capable of crosslinking when mixed together, may be placed in separate chambers of the sprayer. When the sprayer is activated, the emergent spray contacts tissue, resulting in mixing and crosslinking of the two solutions to form a coating (for example a hydrogel) on the tissue surface.

In a preferred embodiment, the sprayer comprises separate spray nozzles for each of two or more crosslinkable solutions, with each nozzle surrounded by a separate or common gas flow outlet. The crosslinkable solutions are stored in separate compartments, e.g., a multi-cylinder syringe, and

communicated under pressure to the spray nozzles. In the presence of gas flow through the gas flow outlets, the crosslinkable solutions are atomized and mixed in the gas flow to form a spray, which may be used to coat tissue. In an alternative embodiment, the gas flow is mixed with the crosslinkable solutions to both propel the solutions out of the spray nozzles and atomize the solutions.

To avoid excessive distention of the tissue cavity surrounding the operative site in laparoscopic applications, the sprayer preferably includes a vent system that vents excess pressure from the tissue cavity. In addition, to avoid backflow into the compartments storing the crosslinkable solutions when the sprayer is first introduced into an insufflated tissue cavity, the supply lines preferably include one-way valves that permit flow through the supply line in the distal direction, but prevent backflow.

The crosslinkable solutions used with the apparatus may be crosslinked using either physical crosslinking, chemical crosslinking, or both. For a chemical initiation process, the two or more crosslinkable solutions may polymerize when mixed in the gas flows during spraying, thus forming an adherent coating that adheres to the tissue surface on contact. If a thermal initiating process is used, the two or more solutions may crosslink after contacting the tissue surface and warming to physiological temperatures.

Alternatively, the two or more solutions may include macromers that contain groups that demonstrate activity towards other functional groups such as amines, imines, thiols, carboxyls, isocyanates, urethanes, amides, thiocyanates, hydroxyls, etc., which

may be naturally present in, on, or around tissue or may be optionally provided in the region as part of the instilled formulation required to effect the barrier.

Methods of forming tissue adherent barriers in accordance with the principles of the present invention also are provided.

Brief Description Of The Drawings

Further features of the invention, its nature and various advantages will be more apparent from the accompanying drawings and the following detailed description of the preferred embodiments, in which:

FIGS. 1A, 1B and 1C, are, respectively, a perspective view of a two-fluid sprayer of the present invention, a detailed view of the distal end of the sprayer, and an end view of the distal end of the sprayer taken along line 1C--1C of FIG. 1A;

FIG. 1D is an end view of the distal end of an alternative embodiment of the sprayer of FIG. 1A taken along line 1C--1C;

FIGS. 2A, 2B and 2C, are, respectively, a perspective view of an alternative embodiment of the two-fluid sprayer of the present invention, a detailed view of the distal end of the sprayer, and an end view of the distal end of the sprayer taken along line 2C--2C of FIG. 2A;

FIG. 2D is an end view of the distal end of an alternative embodiment of the sprayer of FIG. 2A taken along line 2C--2C;

FIGS. 3A and 3B, are respectively, a partially cut-away side and a sectional end view of an alternative embodiment suitable for use in laparoscopic applications; and

FIGS. 4A and 4B, are respectively, a partially cut-away side and a sectional end view of a further alternative embodiment suitable for use in laparoscopic applications.

Detailed Description Of The Invention

The present invention is directed to the use of multi-component crosslinkable solutions to form protective coatings on tissue, e.g., to prevent post-surgical adhesions, or as drug delivery layers. In accordance with the methods of the present invention, two or more crosslinkable solutions are sprayed onto tissue during, or near the completion, of surgery to form adherent coatings.

The following written description describes multi-component hydrogel systems suitable for such use, apparatus for dispensing such hydrogel systems, and provides an illustrative example of use of the inventive methods and apparatus.

Hydrogel Systems Suitable For Use

Crosslinkable solutions preferred for use in accordance with the principles of the present invention include those that may be used to form coatings on tissue, and may form physical crosslinks, chemical crosslinks, or both. Physical crosslinks may result from complexation, hydrogen bonding, desolvation, Van der Waals interactions, ionic bonding, etc., and may be initiated by mixing two components that are physically separated until combined in situ, or as a consequence of a prevalent condition in the physiological environment, such as temperature, pH, ionic strength, etc. Chemical crosslinking may be accomplished by any of a number of mechanisms, including free radical

polymerization, condensation polymerization, anionic or cationic polymerization, step growth polymerization, etc.

Hydrogels suitable for use in accordance with the principles of the present invention preferably crosslink spontaneously without requiring the use of a separate energy source. Such systems allow good control of the crosslinking process, because gelation does not occur until the sprayer is actuated and mixing of the two solutions takes place. If desired, one or both crosslinkable solutions may contain dyes or other means for visualizing the hydrogel coating. Alternatively, a colored compound may be produced as a byproduct of the reactive process. The crosslinkable solutions also may contain a bioactive drug or therapeutic compound that is entrapped in the resulting coating, so that the coating becomes a drug delivery layer.

Properties of the hydrogel system, other than crosslinkability, preferably should be selected according to the intended application. For example, if the sprayer is to be used to provide a tissue adherent coating in the abdominal cavity to prevent post-surgical tissue adhesion, it is preferable that the hydrogel system have a relatively low tensile strength, to avoid adversely effecting normal physiologic processes of the organs, be near equilibrium hydration when formed, experience relatively little in situ swelling, and be biodegradable.

Other applications may require different characteristics of the hydrogel system. There is extensive literature describing the formulation of crosslinkable coating materials for particular medical applications, which formulae may be readily adapted for

use herein with little experimentation. More generally, for example, if a hydrogel system is to be used for coating of tissues, cells, medical devices, or capsules, for drug delivery or as mechanical barriers or supports, the materials should be selected on the basis of exhibited biocompatibility and lack of toxicity. For all biologically-related uses, toxicity must be low or absent in the finished state for externally coated non-living materials, and at all stages for internally-applied materials.

Additionally, the hydrogel system solutions should not contain harmful or toxic solvents. Preferably, the solutions are substantially soluble in water to allow application in a physiologically-compatible solution, such as buffered isotonic saline. Water-soluble coatings may form thin films, but more preferably form three-dimensional gels of controlled thickness. It is also preferable in cases that the coating be biodegradable, so that it does not have to be retrieved from the body. Biodegradability, as used herein, refers to the predictable disintegration of the coating into molecules small enough to be metabolized or excreted under normal physiological conditions.

<u>Polymers Suitable for Physical Crosslinking</u>

Physical crosslinking may be intramolecular or intermolecular or in some cases, both. For example, hydrogels can be formed by the ionic interaction of divalent cationic metal ions (such as Ca+2 and Mg+2) with ionic polysaccharides such as alginates, xanthan gums, natural gum, agar, agarose, carrageenan, fucoidan, furcellaran, laminaran, hypnea, eucheuma, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust beam gum, arabinogalactan, pectin, and amylopectin.

These crosslinks may be easily reversed by exposure to species that chelate the crosslinking metal ions, for example, ethylene diamine tetraacetic acid. Multifunctional cationic polymers, such as poly(l-lysine), poly(allylamine), poly(ethyleneimine), poly(guanidine), poly(vinyl amine), which contain a plurality of amine functionalities along the backbone, may be used to further induce ionic crosslinks.

Hydrophobic interactions are often able to induce physical entanglement, especially in polymers, that induces increases in viscosity, precipitation, or gelation of polymeric solutions. For example, poly(oxyethylene)-poly(oxypropylene) block copolymers, available under the trade name of PLURONIC®, BASF Corporation, Mount Olive, NJ, are well known to exhibit a thermoreversible behavior in solution. Thus, an aqueous solution of 30% PLURONIC® F-127 is a relatively low viscosity liquid at 4°C and forms a pasty gel at physiological temperatures due to hydrophobic interactions. Other block and graft copolymers of water soluble and insoluble polymers exhibit similar effects, for example, copolymers of poly(oxyethylene) with poly(styrene), poly(caprolactone), poly(butadiene) etc.

Techniques to tailor the transition temperature, i.e. the temperature at which an aqueous solution transitions to a gel due to physical linking, are per se known. For example, the transition temperature may be lowered by increasing the degree of polymerization of the hydrophobic grafted chain or block relative to the hydrophilic block. Increase in the overall polymeric molecular weight, while keeping the hydrophilic: lipophilic ratio unchanged also leads to a lower gel transition temperature, because the

polymeric chains entangle more effectively. Gels likewise may be obtained at lower relative concentrations compared to polymers with lower molecular weights.

Solutions of other synthetic polymers such as poly(N-alkylacrylamides) also form hydrogels that exhibit thermoreversible behavior and exhibit weak physical crosslinks on warming. During spraying of thermoreversible solutions, cooling of the solutions may be expected from evaporation during atomization. Upon contact with tissue target at physiological temperatures, viscosity is expected to increase from the formation of physical crosslinks. Similarly, pH responsive polymers that have a low viscosity at acidic or basic pH may be employed, and exhibit an increase in viscosity upon reaching neutral pH, for example, due to decreased solubility.

For example, polyanionic polymers such as poly(acrylic acid) or poly(methacrylic acid) possess a low viscosity at acidic pHs that increases as the polymers become more solvated at higher pHs. The solubility and gelation of such polymers further may be controlled by interaction with other water soluble polymers that complex with the polyanionic polymers. For example, it is well known that poly(ethylene oxides) of molecular weight over 2,000 dissolve to form clear solutions in water. When these solutions are mixed with similar clear solutions of poly(methacrylic acid) or poly(acrylic acid), however, thickening, gelation, or precipitation occurs depending on the particular pH and conditions used (for example see Smith et al., "Association reactions for poly(alkylene oxides) and poly(carboxylic acids)," *Ind. Eng. Chem.*, 51:1361 (1959). Thus, a two component aqueous solution

system may be selected so that the first component (among other components) consists of poly(acrylic acid) or poly(methacrylic acid) at an elevated pH of around 8-9 and the other component consists of (among other components) a solution of poly(ethylene glycol) at an acidic pH, such that the two solutions on being combined in situ result in an immediate increase in viscosity due to physical crosslinking.

Physical gelation also may be obtained in several naturally existing polymers too. For example gelatin, which is a hydrolyzed form of collagen, one of the most common physiologically occurring polymers, gels by forming physical crosslinks when cooled from an elevated temperature. Other natural polymers, such as glycosaminoglycans, e.g., hyaluronic acid, contain both anionic and cationic functional groups along each polymeric chain. This allows the formation of both intramolecular as well as intermolecular ionic crosslinks, and is responsible for the thixotropic (or shear thinning) nature of hyaluronic acid. The crosslinks are temporarily disrupted during shear, leading to low apparent viscosities and flow, and reform on the removal of shear, thereby causing the gel to reform.

Macromers Suitable for Chemical Crosslinking

Water soluble polymerizable polymeric monomers having a functionality >1 (i.e., that form crosslinked networks on polymerization) and that form hydrogels are referred to hereinafter as "macromers". Several functional groups may be used to facilitate chemical crosslinking reactions. When these functional groups are self condensible, such as ethylenically unsaturated functional groups, the crosslinker alone is

sufficient to result in the formation of a hydrogel, when polymerization is initiated with appropriate agents. Where two solutions are employed, each solution preferably contains one component of a co-initiating system and crosslink on contact. The solutions are stored in separate compartments of a sprayer, and mix either when sprayed or on contact with the tissue.

An example of an initiating system suitable for use in the present invention is the combination of a peroxygen compound in one solution, and a reactive ion, such as a transition metal, in another. Other means for polymerization of macromers to coatings on tissue also may be advantageously used with macromers that contain groups that demonstrate activity towards functional groups such as amines, imines, thiols, carboxyls, isocyanates, urethanes, amides, thiocyanates, hydroxyls, etc., which may be naturally present in, on, or around tissue. Alternatively, such functional groups optionally may be provided in the region as part of the instilled formulation required to effect the barrier. In this case, no external initiators of polymerization are needed and polymerization proceeds spontaneously when two complementary reactive functional groups containing moieties interact at the application site.

Preferred hydrogel systems are those biocompatible multi-component systems that spontaneously crosslink when the components are mixed, but wherein the two or more components are individually stable for the duration of the deposition process. Such systems include, for example, contain macromers that are di or multifunctional amines in one component and di or multifunctional oxirane containing moieties

in the other component. Other initiator systems, such as components of redox type initiators, also may be used. The mixing of the two or more solutions may result in either an addition or condensation polymerization that further leads to the formation of a coating.

Any monomer capable of being crosslinked to form a biocompatible surface coating may be used. The monomers may be small molecules, such as acrylic acid or vinyl caprolactam, larger molecules containing polymerizable groups, such as acrylate-capped polyethylene glycol (PEG-diacrylate), or other polymers containing ethylenically-unsaturated groups, such as those of U.S. Patent No. 4,938,763 to Dunn et al, U.S. Patent Nos. 5,100,992 and 4,826,945 to Cohn et al, U.S. Patent Nos. 4,741,872 and 5,160,745 to De Luca et al., or U.S. 5,410,016 to Hubbell et al.

Preferred monomers are the crosslinkable, biodegradable, water-soluble macromers described in U.S. Patent No. 5,410,016 to Hubbell et al, which is incorporated herein by reference. These monomers are characterized by having at least two polymerizable groups, separated by at least one degradable region. When polymerized in water, they form coherent gels that persist until eliminated by self-degradation. In the most preferred embodiment, the macromer is formed with a core of a polymer that is water soluble and biocompatible, such as the polyalkylene oxide polyethylene glycol, flanked by hydroxy acids such as lactic acid, having acrylate groups coupled thereto. Preferred monomers, in addition to being biodegradable, biocompatible, and non-toxic, also will be at least somewhat elastic after polymerization or curing.

It has been determined that monomers with longer distances between crosslinks are generally softer, more compliant, and more elastic. Thus, in the polymers of Hubbell, et al., increased length of the water-soluble segment, such as polyethylene glycol, tends to enhance elasticity. Molecular weights in the range of 10,000 to 35,000 of polyethylene glycol are preferred for such applications, although ranges from 3,000 to 100,000 also are useful.

In addition, coatings formed in accordance with the methods of the present invention may be formed as laminates (i.e., having multiple layers). Thus, for example, a lower layer of the laminate may consist of a more tightly crosslinked hydrogel that provides good adherence to the tissue surface and serves as a substrate for an overlying compliant coating to reactively bond thereto. Materials having lower molecular weights between crosslinks may be suitable for use as a base coating layer. Molecular weights in the range of 400 to 20,000 of polyethylene glycol are preferred for such applications, although ranges from 400 to 10,000 are more preferable.

It should be understood, however, that hydrogels that crosslink by a variety of other mechanisms, for example, by interaction of electrophilic and nucleophilic functional groups, also may be advantageously used in accordance with the principles of the present invention.

Initiating Systems

Metal ions may be used either as an oxidizer or a reductant in redox initiating systems. For example, in the Example set forth hereinbelow, ferrous ions are used in combination with a peroxide or

hydroperoxide to initiate polymerization, or as parts of a polymerization system. In this case, the ferrous ions serve as a reductant. In other previously known initiating systems, metal ions serve as an oxidant.

For example, the ceric ion (4+ valence state of cerium) interacts with various organic groups, including carboxylic acids and urethanes, to remove an electron to the metal ion, and leave an initiating radical behind on the organic group. In such a system, the metal ion acts as an oxidizer. Potentially suitable metal ions for either role are any of the transition metal ions, lanthanides and actinides, which have at least two readily accessible oxidation states.

Preferred metal ions have at least two states separated by only one difference in charge. Of these, the most commonly used are ferric/ferrous; cupric/cuprous; ceric/cerous; cobaltic/cobaltous; vanadate V vs. IV; permanganate; and manganic/manganous. Peroxygen containing compounds, such as peroxides and hydroperoxides, including hydrogen peroxide, t-butyl hydroperoxide, t-butyl peroxide, benzoyl peroxide, cumyl peroxide, etc., may be used.

Thermal initiating systems may be used rather than the redox-type systems described hereinabove. Several commercially available low temperature free radical initiators, such as V-044, available from Wako Chemicals USA, Inc., Richmond, VA, may be used to initiate free radical crosslinking reactions at body temperatures to form hydrogel coatings with the aforementioned monomers.

Preferred macromers for use in forming tissue coatings using the apparatus of the present invention include any of a variety of in situ crosslinkable

macromers that form hydrogel compositions in vivo. These macromers may, for example, be selected from compositions that are biodegradable, crosslinkable, and substantially water soluble macromers comprising at least one water soluble region, at least one degradable region, and statistically more than 1 polymerizable region on average per macromer chain, wherein the polymerizable regions are separated from each other by at least one degradable region. Alternatively, if biodegradability is not desirable, compositions that do not contain the biodegradable segments but are substantially water soluble and crosslink in vivo under acceptable physiological conditions may be used.

Sprayers For Dispensing Hydrogel Coatings

Referring now to FIGS. 1A, 1B and 1C, an illustrative embodiment of a sprayer constructed in accordance with the principles of the present invention is described. Sprayer 10 comprises body 11 having elongated barrel 12, syringes 13 and 14, actuator 15 and gas inlet port 16 coupled to compressor 17 via flexible hose 18. Distal end 19 of sprayer 10 includes outlet nozzles 20a and 20b surrounded by gas flow outlets 21a and 21b, respectively. Compressor 17 supplies a gas flow, preferably compressed air or carbon dioxide, to sprayer 10 either continuously, or when activated by footpedal 22. Gas inlet port 16 may include filter 16a to remove particulate contaminants, including bacteria and other microorganisms, from the gas flow.

Body 11 includes compartments 23 into which syringes 13 and 14 are placed so that the outlets of the syringes are coupled in fluid communication with the interior of tubes 24 and 25, respectively. Each of

syringes 13 and 14 includes plunger 26 that may be engaged in recesses 27 of actuator 15. Accordingly, when actuator 15 is depressed, an equal volume of crosslinkable solution is dispensed from each of syringes 13 and 14. Alternatively, for some systems it may be desirable to omit actuator 15 and instead spray the crosslinkable solutions onto the tissue in a sequential fashion. In either case, sterile crosslinkable solutions may be stored separately in syringes 13 and 14, and assembled in sprayer 10 as required for a particular application.

Tube 24 extends from the proximal end of barrel 12, where it is coupled to syringe 13, to a point a slightly beyond distal endface 28 of barrel 12, where it forms outlet nozzle 20a. Tube 24 is disposed within lumen 29 that communicates with gas inlet port 16. Gas entering sprayer 10 via gas inlet port 16 flows through the annular space defined by the exterior of tube 24 and the interior surface of lumen 29, exiting sprayer 10 through gas flow outlet 21a. As the gas, preferably air or carbon dioxide, flows through gas flow outlet 21a, it mixes with the crosslinkable solution from syringe 13 passing through outlet nozzle 20a, breaking the crosslinkable solution into fine droplets or a mist.

Likewise, tube 25 extends from the proximal end of barrel 12, where it is coupled to syringe 14, to a point a slightly beyond distal endface 28 of barrel 12, where it forms outlet nozzle 20b. Tube 25 is disposed within lumen 30 that communicates with gas inlet port 16. Thus, gas entering sprayer 10 via gas inlet port 16 flows through the annular space defined by the exterior of tube 25 and the interior surface of lumen 30, exiting sprayer 10 through gas flow outlet

21b. As the gas flows through gas flow outlet 21b, it mixes with the crosslinkable solution from syringe 14 passing through outlet nozzle 20b, also breaking the crosslinkable solution into fine droplets or a mist.

Outlet nozzles 20a and 20b are preferably arranged so that the crosslinkable droplets or mist formed by outlet nozzle 20a and gas flow outlet 21a converges with that formed by outlet nozzle 20b and gas flow outlet 21b to provide a spray containing a mixture of the two crosslinkable solutions. As described hereinabove, the two solutions may either crosslink on contact within the spray, or crosslink upon contacting the tissue. Outlet nozzles 20a and 20b may extend several millimeters beyond distal endface 28 of barrel 12 to prevent clogging of the nozzles by premature crosslinking of the emergent fluids by cross-contamination.

Alternatively, it may be desirable to have outlet nozzles 20a and 20b approximately even with distal endface 28 of barrel 12 to reduce the gas flow rate required to entrain and atomize the solutions. Accordingly, outlet nozzles 20a and 20b and gas flow outlets 21a and 21b may be configured so that the movement of the gas flows from gas flow outlets 21a and 21b cause the crosslinkable solutions to be drawn out of nozzles 20a and 20b and entrained in the gas flows by a Venturi effect. In this case, no manual actuation or compression of the crosslinkable solutions is required, and plungers 26 and actuator 15 may be omitted. As a further alternative, instead of using footpedal 22 to regulate the gas flow, compressor 17 may be regulated with a valve (not shown) disposed on body 11 or barrel 12, that selectively diverts gas flow from lumens 29 and 30. This feature may be

particularly useful when the sprayer is used in closed relatively fluid tight cavities, such as the pneumoperitoneum created during laparoscopic or pelvic surgery.

Body 11, barrel 12 and actuator 15 preferably are constructed from a plastic such a polyethylene, while tubes 24 and 25 preferably comprise a rigid material, such as stainless steel. Syringes 13 and 14 may comprise materials typically used in medical devices, while compressor 17 and flexible hose 18 may be of the type commercially available, for example, that are used with airbrushes.

In operation, sprayer 10 is coupled to compressor 17 via flexible hose 18. Syringes 13 and 14 are inserted into compartments 23 of body 11 and plungers 26 of syringes 13 and 14 are engaged in recesses 27 in actuator 15. Distal end 19 of sprayer 10 is disposed within a body cavity, for example, intraoperatively in the abdomen or laparoscopically in the pneumoperitoneum, a few inches from tissue to be coated. Footpedal 22 is then depressed to activate compressor 17, while actuator 15 is depressed to dispense crosslinkable solutions from outlet nozzles 20a and 20b. As the solutions emerge from nozzles 20a and 20b, they are atomized and partially or completely mixed, and directed onto the tissue to be coated. As a result of crosslinking, for example, induced by free radical or chemical crosslinking, the solutions form a film that adheres to the tissue to provide a therapeutic benefit. Alternatively, the solutions may be mixed when they contact the tissue surface.

In FIG. 1D, an alternative embodiment is depicted in which barrel 12' includes outlet nozzles 20a' and 20b' disposed within single gas flow outlet

21a' and gas flow lumen 29'. Operation of this alternative embodiment is similar to that described hereinabove, except that the crosslinkable solutions are entrained from outlet nozzles 20a' and 20b' by a single stream of gas exiting gas flow outlet 21a'. In addition, the sprayer may include a valve or valves (not shown) for regulating the amount of crosslinkable solution and gas existing outlet nozzles 20a', 20b' and 21a', respectively. Such valves also may permit a jet of gas to be directed onto a targeted tissue, for example, to displace saline or body fluids to dry or clean the target tissue prior to instillation of the hydrogel barrier.

Referring now to FIGS. 2A, 2B and 2C, an alternative embodiment of a sprayer of the present invention for forming adherent tissue coatings from a three-part hydrogel system is described. Sprayer 40 comprises body 41 having elongated barrel 42, syringes 43, 44 and 45, actuator 46 and gas inlet port 47 coupled compressed gas cylinder 48. Distal end 49 of sprayer 40 includes outlet nozzles 50a, 50b and 50c surrounded by gas flow outlets 51a, 51b and 51c, respectively. Compressed gas cylinder 48 is coupled to gas inlet port 47 via valve 52 and filter 53. Valve 52 is configured, for example, so that it may be selectively opened or closed by rotating the valve a half-turn. Filter 53 serves the same functions as filter 16a in the embodiment of FIGS. 1.

Body 41 includes compartments 54 into which syringes 43, 44 and 45 are placed so that the outlets of the syringes are coupled in fluid communication with tubes 55, 56 and 57, respectively. Each of syringes 43-45 includes plunger 58 that may be engaged in recesses 59 of actuator 46. Actuator 46 may link all

three of plungers 58 together for common motion, or may be used to link only two of the plungers together, as illustrated by the dotted line in FIG. 2A. Actuator 46 may therefore be depressed to dispense equal volumes of crosslinkable solution from each of syringes 43-45 or just a subset thereof. As in the embodiment of FIG. 1A, the construction of sprayer 40 permits the sterile crosslinkable solutions to be stored separately in syringes 43-45, and assembled in sprayer 40 as required for a particular application.

Tube 55 extends from the proximal end of barrel 42, where it is coupled to syringe 43, to a point a slightly beyond distal endface 60 of barrel 42, where it forms outlet nozzle 50a. Tube 55 is disposed within lumen 61 that communicates with gas inlet port 47. Gas entering sprayer 40 via gas inlet port 47 flows through the annular space defined by the exterior of tube 55 and the interior surface of lumen 61, exiting sprayer 40 through gas flow outlet 51a. As the gas, preferably air or carbon dioxide, flows through gas flow outlet 51a, it mixes with the crosslinkable solution from syringe 43 passing through outlet nozzle 50a, and atomizes the crosslinkable solution into fine droplets or a mist. Tube 56, disposed in lumen 62, and tube 57, disposed in lumen 63, are similarly arranged to atomize crosslinkable solutions from syringes 44 and 45 in the gas flows exiting gas flow outlets 51b and 51c.

Outlet nozzles 50a-50c are preferably arranged so that the atomized crosslinkable solutions converge to provide a spray containing a mixture of the crosslinkable solutions. As in the previous embodiment, outlet nozzles 50a-50c preferably extend several millimeters beyond distal endface 60 of barrel

42 to prevent clogging of the nozzles by premature crosslinking of the emergent fluids by cross-contamination. Alternatively, outlet nozzles 50a-50c and gas flow outlets 51a-51c may be configured so that the gas exiting gas flow outlets 51a-51c cause the crosslinkable solutions to be drawn out of the nozzles by a Venturi effect, as described hereinabove.

With respect to FIG. 2D, an alternative embodiment is depicted in which barrel 42' includes outlet nozzles 50a', 50b' and 50c' disposed within single gas flow outlet 51a' and gas flow lumen 61'. Operation of this alternative embodiment is similar to that described hereinabove, except that the crosslinkable solutions are entrained from outlet nozzles 50a', 50b' and 50c' by a single stream of gas exiting gas flow outlet 51a'. In addition, like the embodiment described with respect to FIG. 1D, the sprayer may include a valve or valves for regulating the amount of crosslinkable solution and gas existing the outlet nozzles, and also may permit a jet of gas to be directed onto a targeted tissue to displace saline or body fluids, thereby drying or cleaning the target tissue prior to instillation of the hydrogel barrier.

The embodiments of FIGS. 2 may be advantageously used to dispense a three component hydrogel system to form an adherent therapeutic layer on a tissue surface. Alternatively, syringes 43 and 44 may contain components of crosslinkable solution that are activated to initiate crosslinking by mixing the two solutions. Syringe 45 may then contain a further crosslinkable solution that enhances adherence of the coating to tissue, for example, by providing a highly crosslinked network as the base coat or by helping the

top coat adhere better to the tissue surface by other mechanisms.

Referring now to FIGS. 3A and 3B, a further alternative embodiment of the sprayer of the present invention is described which is adapted for use in laparoscopic applications. Sprayer 70 comprises body 71 having elongated barrel 72, material supply ports 73 and 74, an actuator (not shown) and gas inlet port 75 coupled to a source of compressed gas or a compressor (not shown) via filter 76 and flexible hose 77. Supply port 73 is coupled to nozzle 78 by supply line 79 while supply port 74 is coupled to nozzle 80 by supply line 81. Gas inlet port 75 is coupled by hose 77 to nozzle 82 disposed in chamber 83. Gas exiting nozzle 82 flows into chamber 83, and then exits chamber 83 by flowing through annular gaps 84 surrounding nozzles 78 and 80, as for the embodiment of FIG. 1.

Reservoirs of crosslinkable solutions are coupled to supply ports 73 and 74, so that when sprayer 70 is actuated, compressed gas flowing around nozzles 78 and 80 draws the crosslinkable solutions through supply lines 79 and 81. The gas flow exiting through annular gaps 84 atomizes and mixes the crosslinkable solution, and deposits the crosslinkable solutions onto a target tissue.

In accordance with one aspect of the present invention, one-way valves 85 are disposed on supply lines 79 and 81 to prevent backflow of insufflation gases in a tissue cavity from charging the reservoirs of crosslinkable solutions. More specifically, one-way valves permit flow through the supply lines from the reservoirs to nozzles 78 and 80, but prevent the backflow of insufflation gases in a tissue cavity from flowing into the reservoirs when the sprayer is first

introduced into the tissue cavity. Additionally, one-way valves prevent compressed gas from the sprayer from being directed through the supply lines if, for example, if the distal end of the sprayer were pushed into tissue or otherwise blocked.

During laparoscopic surgery, for example, in the peritoneal cavity, it is typical to employ an insufflator to create a gas-filled cavity in which the surgeon can view and manipulate his or her instruments. Such devices inject a pressurized gas, such as carbon dioxide, and monitor and regulate the insufflation pressure by adding additional carbon dioxide to compensate for any leakage. Once a patient is insufflated, experienced surgeons typically maintain the insufflation without requiring much additional carbon dioxide.

Because the methods and apparatus of the present invention employ a pressurized gas to atomize and deposit the crosslinkable solution, however, a vent system must be provided to prevent excessive distension of the tissue cavity. Accordingly, sprayer 70 includes one or more vent holes 86 that communicate with bore 87 of elongated barrel 72 and proximal vent holes 88 in body 71. Vent holes 86 and proximal holes 88 permit excess gas pressure to be vented from the tissue cavity through the sprayer. While carbon dioxide will leak from the peritoneal cavity through vent holes 86 and 88, when there is no gas flow from the sprayer, applicants do not expect this leakage to present a problem, because the insufflator will add additional carbon dioxide to compensate for this leakage.

In operation, sprayer 70 is coupled to a source of compressed gas or a compressor via filter 76 and hose 77. Reservoirs of crosslinkable solutions are

coupled to supply ports 73 and 74. The distal end of sprayer 70 then is disposed within a body cavity, for example, intraoperatively in the abdomen or laparoscopically in the pneumoperitoneum, a few inches from tissue to be coated. When sprayer 70 is actuated, for example, by a footpedal (not shown) coupled to the compressor or source of compressed gas, crosslinkable solutions from nozzles 78 and 80 by gas exiting through annular gaps 84. As the solutions emerge from nozzles 78 and 80, they are atomized and mixed, and directed onto the tissue to be coated. As a result of crosslinking, for example, induced by free radical or chemical crosslinking, the solutions form a film that adheres to the tissue to provide a therapeutic benefit.

Referring to FIGS. 4A and 4B, another alternative laparoscopic embodiment of the sprayer of the present invention is described. Sprayer 90 comprises body 91 having elongated barrel 92, material supply ports 93 and 94, an actuator (not shown) and gas inlet port 95 coupled to a source of compressed gas or a compressor (not shown) via filter 96 and flexible hose 97. Supply port 93 is coupled to nozzle 98 by supply line 99 while supply port 94 is coupled to nozzle 100 by supply line 101. Gas inlet port 95 is coupled by hose 97 to outlet 102 disposed in chamber 103. Gas exiting outlet 102 flows into chamber 103 and then exits chamber 103 by flowing through openings 104 into supply lines 99 and 101.

Reservoirs of crosslinkable solutions are coupled to supply ports 93 and 94, so that when sprayer 90 is actuated, gas introduced into chamber 103 enters supply lines 99 and 101 through openings 104, mixes with and atomizes the crosslinkable solutions in the supply lines, and propels the solutions to exit through

nozzles 98 and 100. As the gas flow and solution mixture exits through nozzles 98 and 100, it further atomizes and mixes the crosslinkable solutions, and deposits the solutions onto a target tissue.

As for the embodiment of FIGS. 3, one-way valves 105 are disposed on supply lines 99 and 101 to prevent backflow of gas from chamber 103 or insufflation gases in a tissue cavity from charging the reservoirs of crosslinkable solutions. More specifically, one-way valves permit flow through the supply lines from the reservoirs to nozzles 98 and 100, but prevent the backflow of insufflation gases in a tissue cavity from flowing into the reservoirs when the sprayer is first introduced into the tissue cavity. Additionally, one-way valves prevent compressed gas from chamber 103 of the sprayer from being directed through the supply lines if, for example, if the distal end of the sprayer were pushed into tissue or otherwise blocked.

In addition, sprayer 90 includes one or more vent holes 106 that communicate via tubing 107 disposed within elongated barrel 92 and proximal vent holes 108 in body 91. Vent holes 106 and proximal holes 108 permit excess gas pressure to be vented from the tissue cavity through the sprayer. While carbon dioxide will leak from the peritoneal cavity through vent holes 106 and 108 when there is no gas flow from the sprayer, applicants do not expect this leakage to present a problem, because the insufflator will add additional carbon dioxide to compensate for this leakage.

In operation, sprayer 90 is coupled to a source of compressed gas or a compressor via filter 96 and hose 97. Reservoirs of crosslinkable solutions are coupled to supply ports 93 and 94. The distal end of

sprayer 90 then is disposed within a body cavity, for example, intraoperatively in the abdomen or laparoscopically in the pneumoperitoneum, a few inches from tissue to be coated. When sprayer 90 is actuated, for example, by a footpedal (not shown) coupled to the compressor or source of compressed gas, gas flows into chamber 103 and through openings 104, mixes with crosslinkable solutions in supply lines 99 and 101, and exits from nozzles 98 and 100. As the gas-solution mixtures emerge from nozzles 98 and 100, they are further atomized and mixed, and directed onto the tissue to be coated. As a result of crosslinking, for example, induced by free radical or chemical crosslinking, the solutions form a film that adheres to the tissue to provide a therapeutic benefit.

The advantages and benefits of the methods and apparatus of the invention are clearly demonstrated by the following example, which is provided for purposes of illustration, and not limitation of the invention. Other such uses will be apparent to those familiar with the art.

Example

Sprayer 10 of FIGS. 1 is used in conjunction with aqueous solutions of crosslinkable monomers. Solution 1, consisting of a 10% solution of a polyethylene glycol diacrylate (M.W. 3,000 Da, purchased from Shearwater Polymers, Huntsville, AL) dissolved in normal saline (pH 5-6) and containing 500 ppm of hydrogen peroxide is drawn up in syringe 13, preferably a 5 cc syringe. Solution 2, consisting of a 10% solution of a polyethylene glycol diacrylate dissolved in normal saline (pH 5-6) and containing 5000 ppm of ferrous sulfate peroxide, is drawn up in syringe

14, also a 5 cc syringe. Syringes 13 and 14 are individually loaded in compartments 23, and are coupled to tubes 24 and 25 and actuator 15.

Airflow from a regulated source of compressed air (an air compressor such as those commercially available for airbrushes) is connected to the sprayer 10 using a piece of tubing. When actuator 15 is depressed, a steady spray of the two liquid components will be observed. When this spray is directed to a piece of tissue a hydrogel coating will be observed to form on the surface of the tissue. The hydrogel coating is resistant to rinsing and is well adhered to the tissue surface. Within a short period of time (less than a minute) an area of 10 cm X 5 cm may be coated with ease.

* * *

While preferred illustrative embodiments of the invention are described above, it will be apparent to one skilled in the art that various changes and modifications may be made therein without departing from the invention and it is intended in the appended claims to cover all such changes and modifications which fall within the true spirit and scope of the invention.

Claims

What Is Claimed Is:

1. Apparatus for forming in situ, in a tissue cavity, a tissue adherent coating from at least first and second solutions, the apparatus comprising:

first and second chambers for storing the first and second solutions;

a first nozzle in fluid communication with the first chamber and adapted to permit the first solution to flow from the first nozzle;

a second nozzle in fluid communication with the second chamber and adapted to permit the second solution to flow from the second nozzle;

a first gas flow outlet, the first gas flow outlet disposed surrounding at least the first nozzle; and

a source of pressurized gas coupled to the first gas flow outlet,

wherein pressurized gas exiting the first gas flow outlet atomizes and mixes the first solution with the second solution.

2. The apparatus of claim 1 further comprising a vent hole for venting excess pressure within the tissue cavity.

3. The apparatus of claim 1 further comprising first and second plungers disposed in the first and second chambers, respectively.

4. The apparatus of claim 3 further comprising a member coupling the first and second plungers together.

5. The apparatus of claim 1 wherein gas flowing from the first gas flow outlet induces a venturi effect that draws the first and second solutions from the first and second nozzles, respectively.

6. The apparatus of claim 1 wherein the source of pressurized gas is a compressor.

7. The apparatus of claim 1 wherein the source of pressurized gas is a compressed gas cylinder.

8. The apparatus of claim 1 wherein the first and second chambers are detachably coupled to the first and second nozzles, respectively.

9. The apparatus of claim 1 further comprising means for selectively coupling the source of pressurized gas to the first gas flow outlet.

10. The apparatus of claim 1 further comprising a second gas flow outlet disposed surrounding the second nozzle.

11. The apparatus of claim 1 further comprising means for controlling a rate at which pressurized gas exits the first gas flow outlet.

12. The apparatus of claim 1 further comprising means for regulating a rate at which the first and second solutions flow from the first and second nozzles, respectively.

13. The apparatus of claim 1 further comprising one-way valves that prevent backflow of a pressurized gas from the tissue cavity into the first and second chambers.

14. Apparatus for forming in situ, in a tissue cavity, a tissue adherent coating from at least first and second solutions, the apparatus comprising:

first and second chambers for storing the first and second solutions;

a third chamber coupled to a source of pressurized gas;

a first nozzle coupled to a first supply line, the first supply line being in fluid communication with the first chamber and having an opening in communication with the third chamber; and

a second nozzle coupled to a second supply line, the second supply line being in fluid communication with the second chamber and having an opening in communication with the third chamber,

wherein pressurized gas entering the third chamber enters the first and second supply lines and propels the first and second solutions out of the first and second nozzles, respectively, to atomize and mixes the first solution with the second solution.

15. The apparatus of claim 14 further comprising a vent hole for venting excess pressure within the tissue cavity.

16. The apparatus of claim 14 further comprising first and second plungers disposed in the first and second chambers, respectively.

17. The apparatus of claim 16 further comprising a member coupling the first and second plungers together.

18. The apparatus of claim 14 wherein the source of pressurized gas is a compressor.

19. The apparatus of claim 14 wherein the source of pressurized gas is a compressed gas cylinder.

20. The apparatus of claim 14 wherein the first and second chambers are detachably coupled to the first and second supply lines, respectively.

21. The apparatus of claim 14 further comprising means for selectively coupling the source of pressurized gas to the third chamber.

22. The apparatus of claim 14 further comprising means for regulating a rate at which the first and second solutions flow from the first and second nozzles, respectively.

23. The apparatus of claim 14 further comprising one-way valves coupled between each one of the first chamber and first supply line and the second chamber and the second supply line.

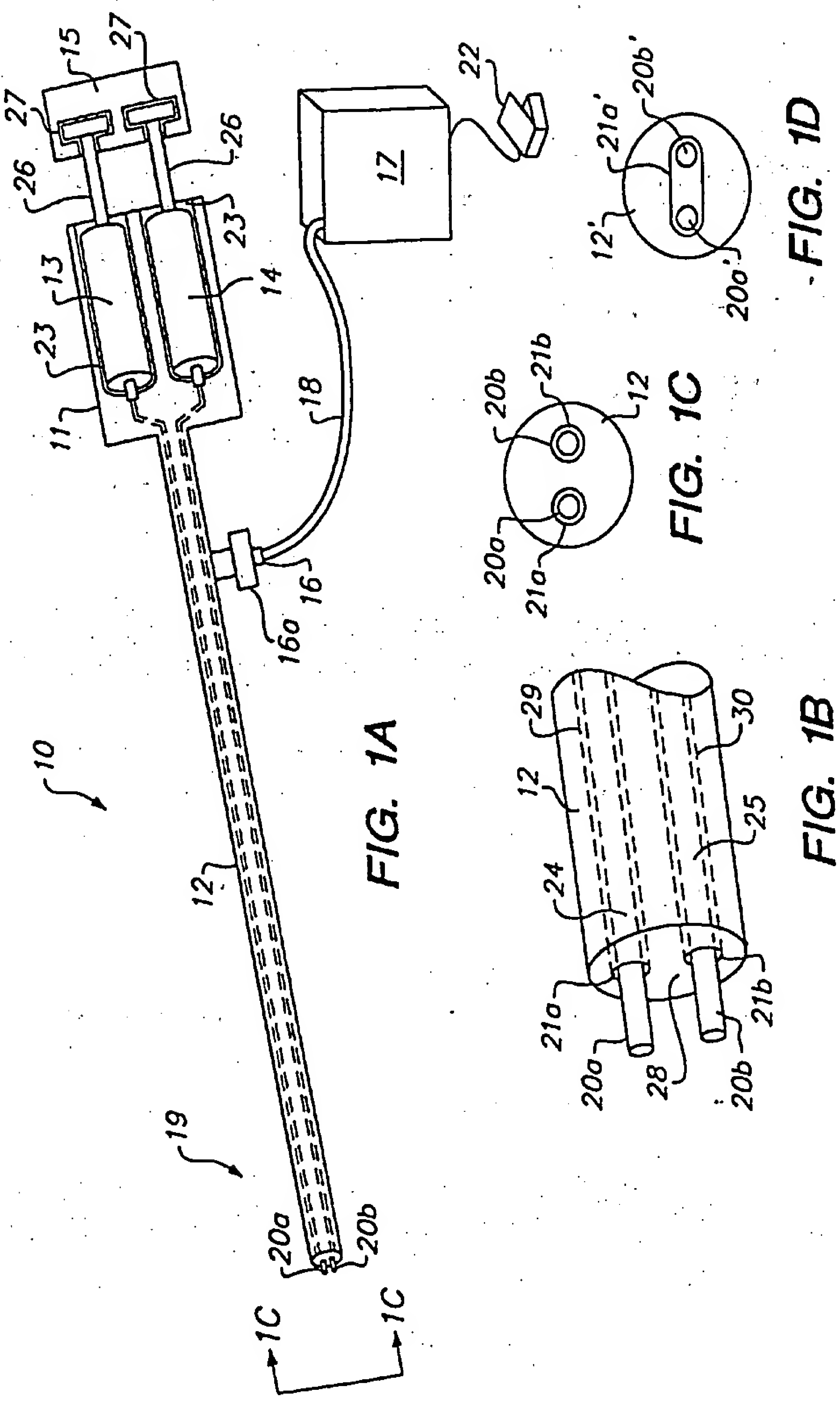

FIG. 1A

FIG. 1B

FIG. 1C

FIG. 1D

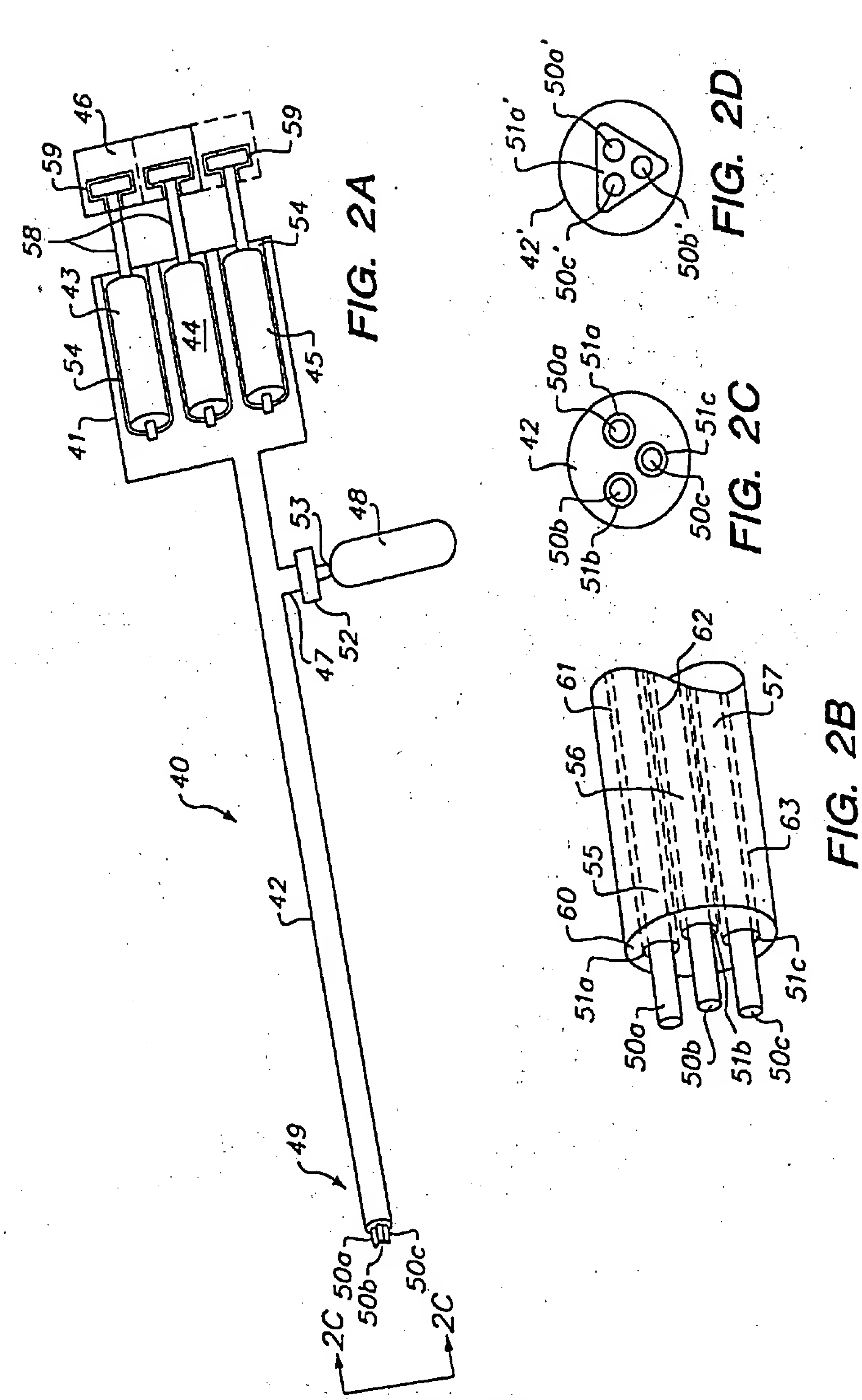

FIG. 2A

FIG. 2B

FIG. 2C

FIG. 2D

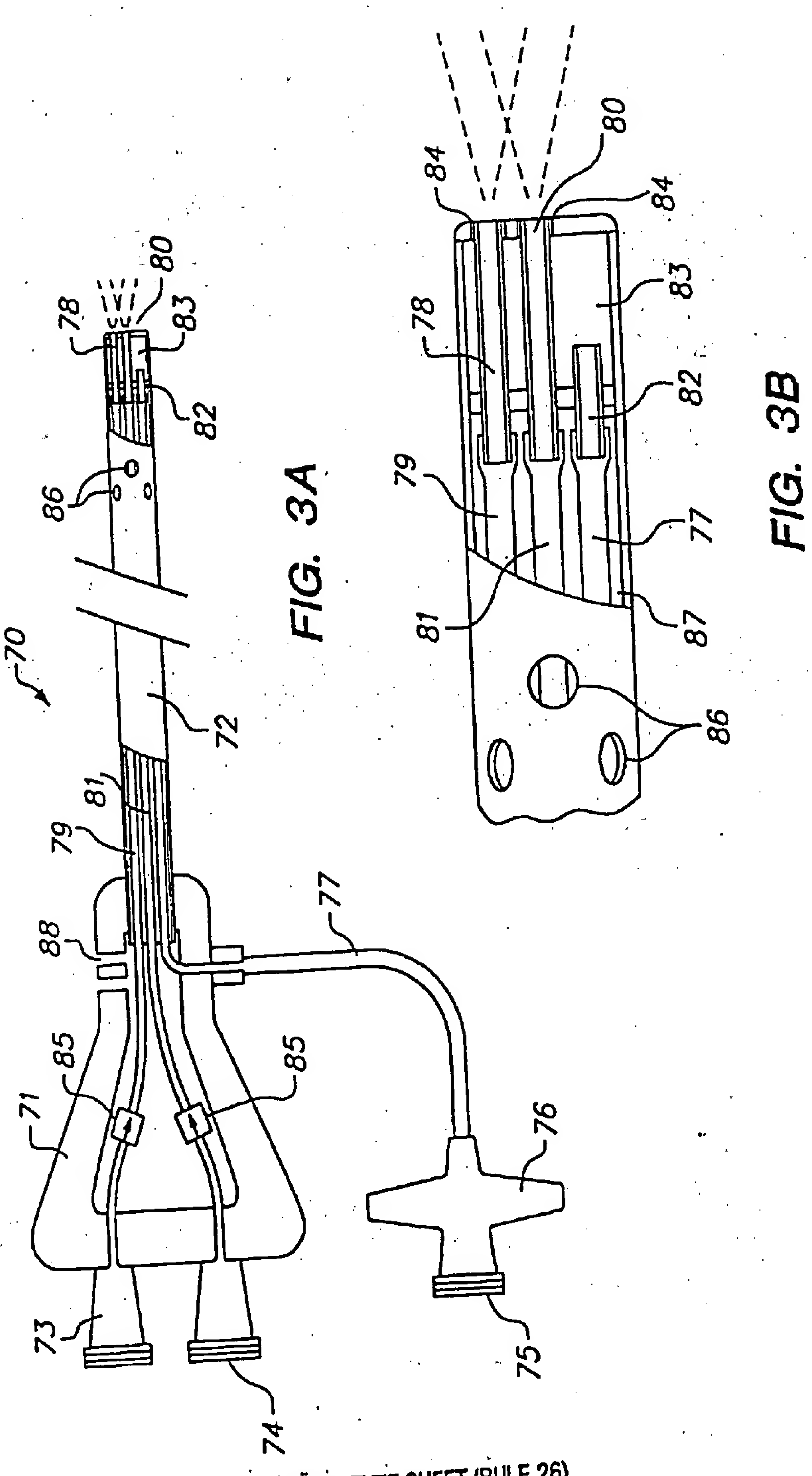

FIG. 3A

FIG. 3B

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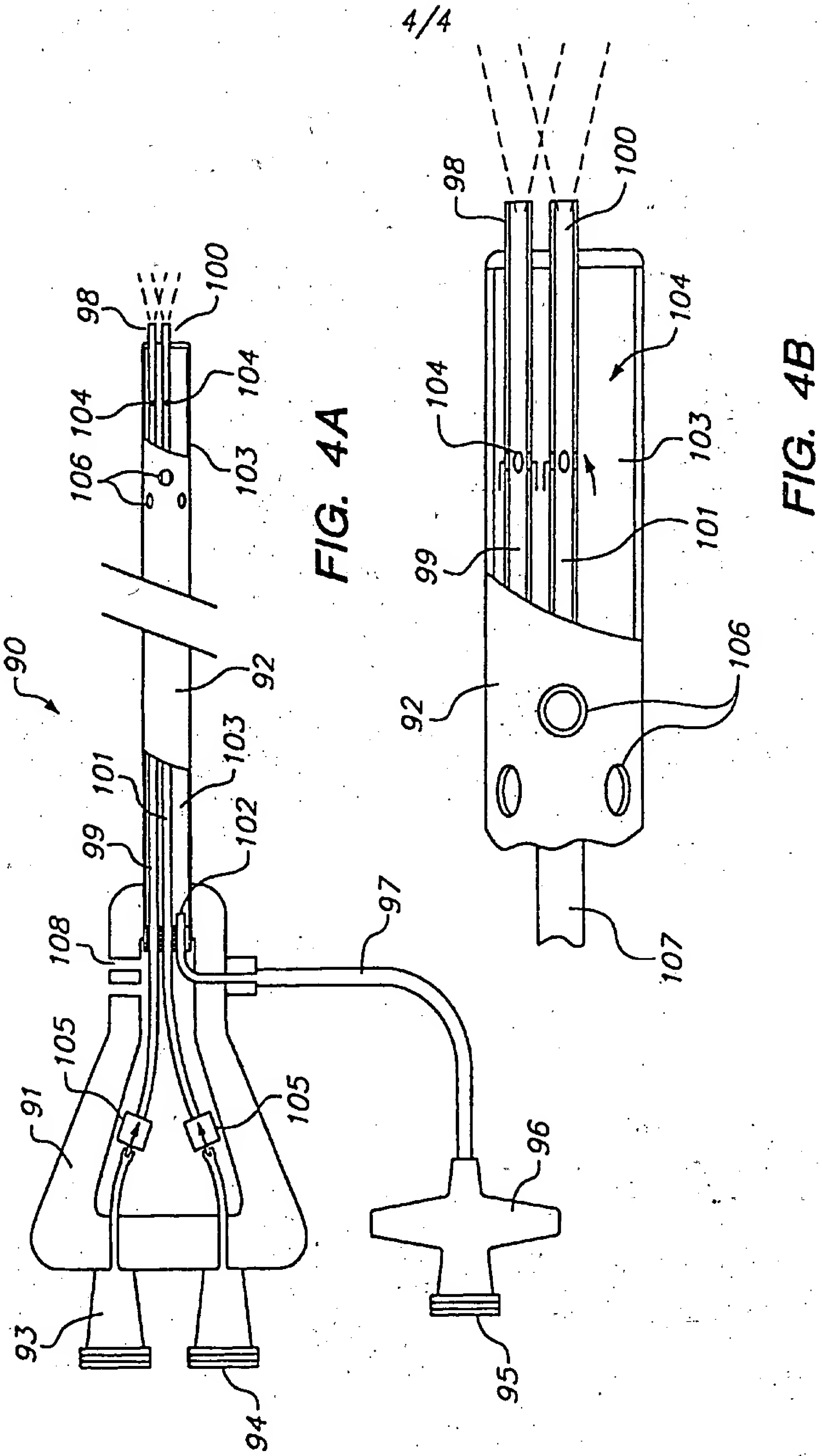

FIG. 4A

FIG. 4B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18446

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61M 37/00
US CL :604/82, 191
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 604/82-84, 94, 131, 191, 218

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 5,582,596 A (FUKUNAGA et al.) 10 December 1996, entire document.	1, 3-14, 16-23 — 2, 15
A	US 5,740,965 A (MIYAGI et al.) 21 April 1998, Abstract.	1-23
A	US 5,759,169 A (MARX) 02 June 1998, Abstract.	1-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 OCTOBER 1999	19 NOV 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON ELIZABETH FINKEL Telephone No. (703) 305-0154